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ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF

INTERNAL SECRETIONS

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RECENT STUDIES ON CHEMICAL MEDIATIONS OF NERVE IMPULSES*

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From the Laboratories of Physiology of the Harvard Medical School

BOSTON

The chemical mediation of nerve impulses by the action of adrenin is well known. Any general stimulation of the sympathetic division of the autonomic nervous system causes a secretion of adrenin, and this adrenin, widely distributed by the blood, has as a rule the same effects as the sympathetic impulses. Thus a viscus, even though deprived of its sympathetic nerves, may be brought into action with the other viscera because adrenin acts as an intermediary between the responsive organ and the nerve impulses which come to the adrenal medulla.

Recent studies have shown that the action of adrenin, as an intermediary agent bringing about effects in the organism equivalent to those caused by nerve impulses, illustrates an extensive phenomenon of such mediation. These recent researches, however, have been concerned with a much more intimate relation between the impulses and the reacting tissues. Indeed, they show that chemical substances are set free by the impulses near or within the cells which make up the tissue. The evidence for this phenomenon was first presented by Loewi (1) in 1921 when he reported that Ringer's solution, which had been in contact with a frog heart subjected to vagus influence, acquired a new property, that of bringing about in another frog heart the inhibitory effect which is characteristic of vagus stimulation. He also showed that if the first heart was stimulated through the sympathetic fibres, the Ringer's solution applied to a second heart would undergo the acceleration characteristic of sympathetic influences. These fundamental observations have been confirmed by numerous investigators and the phenomenon has been observed not only on frog and tortoise hearts but also on the heart of warm-blooded animals (2). Furthermore, it has been reported that the material given off from the heart has typical vagal and sympathetic effects on the stomach and intestine (3). Since the experimental procedure is difficult, there have been, naturally enough, reports of failure to obtain the results described by Loewi and the others who have confirmed his work.

*Read before the Fifteenth Annual Meeting of the Association for the Study of Internal Secretions, Philadelphia, June 8, 1931.

Another forward step was taken last year when Finkelman (4) reported that if Ringer's solution is allowed to run over a pulsating piece of rabbit intestine, A, still supplied with its mesenteric nerves, and pass thence to another piece of pulsating intestine, B, the solution acquires a new property when the nerves of piece A are stimulated—piece A is inhibited and thereby the piece B is inhibited also.

Furthermore, Dale and Gaddum (5) have recently reviewed, repeated and extended the observations of Vulpian (6) and of Sherrington (7) on the curious, slow contraction of denervated skeletal muscle when neighboring parasympathetic nerves are stimulated, and they have offered evidence that the phenomenon can reasonably be explained as due to the effect on the muscle of a chemical substance locally discharged by parasympathetic impulses.

From the foregoing observations it is evident that peculiar substances are given off from or near effector organs innervated by sympathetic and parasympathetic fibres of the autonomic nervous system and that these substances are capable of influencing other organs, similarly innervated, just as the nerve impulses do. Examination of the "vagus stuff," as Loewi calls it, shows that it is dialyzable, insensitive to acid, very sensitive to alkali, and that its activity can be readily destroyed by treatment with a tissue esterase (8). In general, the evidence points directly towards its being a highly unstable and very active ester of choline and possibly acetyl-choline itself. Although it remains stable for a long time in the undisturbed heart, it is rapidly broken down after it is once freed by vagus stimulation or by mincing cardiac tissue (9). In 1901, Hunt (10) found in aqueous extracts of the adrenal gland a blood-pressure reducing substance which on chemical treatment disappeared as the choline content increased. He inferred that in the extracts there was an ester-like "precursor" of choline, and this led him to the synthesis of acetyl-choline and to his later classical studies of the pharmacology of this substance. Dale and Dudley (11) have recently been able to isolate and identify acetyl-choline in extracts of fresh spleen. The high degree of instability of acetyl-choline probably accounts for the failure to identify the substance in tissues until recently.

The accelerator substance, derived from cardiac tissue subjected to sympathetic stimulation, is destroyed when the cardiac contents are ashed. Like adrenin, it is rendered inactive when mixed with eosin and exposed to ultraviolet light (12). Like adrenin, also, the solution from the stimulated heart causes constriction of the frog's arterioles. Like adrenin, it is rendered more effective by a dilute solution of glycocoll, and like adrenin it loses its activity on standing in air for 20 hours or on being heated to 100° C. (13).

It is interesting to observe that the two substances mentioned as being produced by parasympathetic and sympathetic nerve impulses, acetyl-choline and adrenin, respectively, have, when injected into the organism,

the usual effects which are produced by the nerve impulses. If we consider that these substances are set free by the nerve impulses as they come to the effector cells, we may regard the substances as chemical mediators of the impulses.

The point has been made by Demoor that while the phenomena which have been briefly described above are true for isolated cardiac muscle and intestine bathed in Ringer's solution, or at best in a mixture of Ringer's solution and defibrinated blood, there is no clear proof that the phenomena occur under natural conditions. Although arguing for the reality of the humoral transmission of nerve impulses, Demoor has declared, "it is evident that the irrigations of the heart which are a part of all these investigations may create new conditions of existence for the tissues, conditions accompanied by permeabilities which do not exist in physiological states, and that the escape of vagal and sympathetic substances, though proved experimentally, may not occur normally." Evidence that this wise precaution on the part of Demoor may be now set aside, at least with respect to the sympathicomimetic substance, has recently been obtained at the Harvard Physiological Laboratories (15, 16) and I propose now to present that evidence.

For many years the heart isolated from the central nervous system—the "denervated" heart—has been used by us as an indicator of chemical changes occurring in the blood stream. This preparation is very insensitive to alterations of blood pressure, but highly sensitive to circulating adrenin. It will respond with a faster beat to a dilution of adrenin 1 part in 1,400,000,000 parts of blood (17). By means of this delicate indicator, studies have been conducted on the effect of cold, asphyxia, motion and emotion, and other conditions, on secretion from the adrenal medulla.

Although the immediate effect of emotional excitement, for example, disappears when the adrenal glands are rendered inactive by removal of one and denervation of the other, it has been known for some years that there is a slow increase of heart rate which, unlike the quick adrenin effect, reaches its maximum about three minutes after the brief excitement ceases. This curious phenomenon has presented to workers in the laboratory a tantalizing and mysterious problem, and much time and experimentation have been spent in attempts to explain it. The phenomenon continued after exclusion of all known or possible cardio-accelerator agencies. It continued after removal of one adrenal and the medulla of the other, after extirpation of the accessory chromophil substance on the front of the aorta, after denervation of the pancreas and intestinal mucosa, after removal of the pituitary body, the thyroids and the parathyroids, as well as the gonads. When the upper thoracic sympathetic chains had been removed and the two abdominal chains, as well, the phenomenon still persisted. It disappeared on excision of the remnants of the sympathetic in the lower chest and it remained in abeyance for many weeks thereafter. From this observation it was clear that a substance is probably given off into the

blood stream when structures innervated by the sympathetic system are stimulated—a substance which has the accelerating action on the denervated heart that is characteristic of circulating adrenin.

Experimental proof of the actual existence of a circulating mediator of widely distributed sympathetic impulses was difficult to obtain because the anesthetics which were tried abolished the effect of stimuli which might bring the sympathetic system into action. Finally proof was obtained, however, in a preparation in which the heart was denervated, the adrenals and liver excluded from action, and the spinal cord severed in the mid-thoracic region (so as to permit without anesthesia painless operations in the hind part of the animal). With this preparation a stimulation of the sympathetic fibres distributed to the smooth muscles of the tail hairs caused a slow increase of blood pressure and heart rate, reaching a maximum in two or three minutes and gradually returning to the former level. More recently we have found that the anesthetic, "Dial," can be used to produce complete anesthesia without abolishing the phenomenon of remote action of sympathetic influence.

That there really is a substance given off into the blood stream when smooth muscle is subjected to sympathetic control has been proved by checking the blood flow into and from the tail region during the stimulation and then allowing the flow to continue. The rise of blood pressure and the acceleration of the heart are then much reduced or are delayed until the flow is restored. Further proof has lately been obtained by stimulating a part of the lower abdominal sympathetic which causes erection of the hairs in a circumscribed patch of the back of the animal. When this area is removed, precisely the same stimulus as before has no effect.

Since the substance which accelerates the denervated heart—and to this may be added the denervated submaxillary gland and the denervated nictitating membrane—is derived from smooth muscles when they are influenced by sympathetic impulses, we have suggested that it be called "sympathin." Quite possibly sympathin is the same substance as adrenin, but as it has a different source, it may be justifiably given a different name.

In this connection it is of interest to note that cocaine, which greatly sensitizes the smooth muscle of blood vessels to the action of adrenin, has a similar effect on sympathin (18). Quantitation of sympathin in terms of adrenin shows that the total amount of sympathin produced as a consequence of stimulating the tail hairs for a half-minute is equivalent to 0.000005 gram of adrenin.

The two substances, sympathin and adrenin, Rosenblueth and I have recently shown to be coöperative. If the denervated nictitating membrane is used as an indicator and a threshold stimulus for medulliadrenal secretion and sympathin secretion has been established, the consequence of causing a discharge of both sympathin and adrenin with such stimuli is a greatly augmented contraction of the membrane.

The demonstration that sympathin, resulting from the action of sympathetic impulses on smooth muscle, is given off in sufficient quantity to affect through the blood stream distant structures, suggested that by properly contrived experiments the "vagus stuff" could be similarly demonstrated. Freeman, Phillips and I (19), using the completely denervated iris and submaxillary gland, and also the blood pressure, the denervated heart (with intrinsic vagal neurones present) and the denervated tongue, as indicators, tested the effect of stimulating the whole vagal distribution below the cardiac branches. Although we arranged a by-pass for the blood from the portal vein to the inferior cava in order to avoid possible destruction of the vagus substance by the liver, and although we employed various anesthetics and in some experiments excluded the need for anesthesia, all our results were negative. It would appear, therefore, that the influence of the parasympathetic substance is quite local. This conclusion is in harmony with the view that as a rule the parasympathetic nerves distribute directly to the structures innervated and thus are organized for specific innervation of those structures rather than for diffuse effects such as are produced by the sympathetic impulses in coöperation with adrenin and sympathin.

About ten years ago experiments were reported that demonstrated the production of a substance by the liver, when under sympathetic influence, that caused acceleration of the denervated heart (20). The acceleration of the heart produced by sympathin raised the question as to whether the cardio-accelerator substance from the liver might not also be sympathin. This question has not yet been definitely settled. It appears that the liver substance is augmented by eating protein food. Sympathin from smooth muscle does not seem to be influenced in this way. It is true, however, that the substance given off from the liver is capable not only of accelerating the heart but can cause also a rise of blood pressure and a contraction of the denervated nictitating membrane. Further experimenting may prove that the liver gives off sympathin as do other organs innervated by the sympathetic but that the amount given off is affected by the character of the food which has been eaten. Indeed, it is not beyond the bounds of possibility that the liver is a place where sympathin and adrenin are prepared from a simple amino acid closely related to them in chemical structure.

The evidence that adrenin and sympathin are similar if not identical substances has an interesting bearing on an idea expressed by Elliott (21) about twenty-five years ago. Struck by the fact that adrenin has its usual influence on smooth muscle cells though the sympathetic nerve supply has been cut and has degenerated, he concluded that adrenin does not act by exciting a structure derived from, or dependent for its existence on, the peripheral neurone; and he suggested that the muscle cell in response to sympathetic connections develops a local mechanism for receiving and transforming the nerve impulses and that adrenin might be the chemical stimulant that is liberated whenever the nerve impulses arrive at the periphery.

According to this idea, adrenin from the adrenal medulla would mimic the action of sympathetic impulses because it is the same substance as that which mediates the action of nerve impulses on the special mechanism (contraction or inhibition) in the effector cell. Indeed, Elliott in his classic paper of 1905 (22) figures such a cell where the contractile structure lies in a less differentiated mass of cell protoplasm in which, it is assumed, the substance is set free by the nerve impulses. Only a small extension of Elliott's hypothesis is needed to explain the phenomenon of humoral transmission of sympathetic impulses from smooth muscle to other structures under sympathetic control—so much local sympathin might be liberated by the impulses that it overflows the cell boundaries and enters the blood stream. Once in the stream it has the same effects as adrenin.

An alternative idea regarding the relation of nerve ending to effector organ has been suggested by Parker (23). He points out that the shrimp, *Palaemonetes,* which has red-yellow chromatophores, becomes dark when placed in a black dish containing sea water, because of the expansion of these organs, and turns light again if placed in a white dish, because of their contraction. The color changes are dependent upon the animal's eyes, only one of which need be functional. If both eyes are blinded the chromatophores expand and thereafter no change occurs, irrespective of the illumination of the background. Older workers assumed that these changes were brought about by nervous influences affecting the expansile and contractile structures, but Perkins (24) showed that removal of nerve connections did not affect the changes, whereas interference with the blood supply would cause the chromatophores, if not already expanded, to pass quickly into that state and remain so indefinitely. Obviously some agent carried in the blood caused the contraction. Perkins injected watery extracts from many organs of the body of the shrimp, but without success. Finally he discovered that extracts of the eye stalks, injected into *Palaemonetes* that had been blinded and that were therefore dark from expanded chromatophores, caused these cells to become contracted and remain so for about a day. The conclusion was drawn that the eye stalks, when stimulated by light from a white background, produce a substance which passes into the blood and thus excites all over the body a contraction of the chromatophores. These observations are typical of similar observations made on other crustacea—indeed, extracts have been found which will cause both contraction and expansion of the pigment cells. These responses of sensitive effectors to the stimulation of the eye in invertebrates Parker likens to similar phenomena in fishes, amphibians and reptiles. In amphibians, for example, according to Hogben and Slome (25), the chromatophores are controlled not only by nerves but also through the secretion of pituitrin; in these animals, however, as in the crustacea, the eye is essential to the action of the controlling substance. In fishes and reptiles the chromatophores appear to be dominated directly by nerves, but adrenin has the same effect as the nerve impulses, *i.e.,* it causes contraction of the pigment cells. In view of the fact that the chemical sub-

stances which influence chromatophores are of nervous origin—from the eye stalk, for example, in *Palaemonetes,* and from the adrenal medulla and the posterior lobe of the pituitary body—Parker suggests that the agent which acts when nerve impulses arrive at an effector cell is a *secretion of the nerve terminals* and not, therefore, a derivative of the cell itself. In other words, the humoral intermediary between the nerve impulse and the responsive terminal organ lies within the cell, according to Elliott, but is produced by the nerve terminal and affects the cell by entering it, according to Parker.

At present, I do not know of any evidence which will clearly determine which of these two views is correct. The fact that the best known humoral mediators of nerve impulses come from cells of nervous origin favors, by analogy, the production of a substance by the nerves themselves at their terminations. Sympathin might thus be derived from the sympathetic nerve endings. On the other hand, the absence of response of smooth muscle to adrenin when such muscle does not have sympathetic connections (22) indicates that there is a peculiar relation of the sympathetic fibres to the muscle structure and function. Elliott's notion that the nerve and the muscle form a continuous mass and that somehow the fusion of sympathetic axones with smooth muscle gives to the muscle the peculiar property of responding to adrenin, might be interpreted as an endowment of the smooth muscle cell with some of the properties of the nervous structure which Parker postulates. It seems almost impossible that sufficient substance could be produced by the minute nerve terminals to affect not only the immediate cells with which they are in contact, but also other structures distributed widely over the body; as, for example, the fact that sympathin from a small patch of hair on the back acts effectively, after being diluted in the blood stream, on the denervated heart or nictitating membrane. On the other hand, if the substance is produced inside of relatively large smooth muscle cells and there acts on the contractile mechanism, it might readily be produced in such abundance as to escape and have distant effects. Unfortunately the action of drugs does not definitely discriminate between these two views of the humoral mediation of nerve impulses. Ergotamine, for example, will block nerve impulses and also the action of adrenin. It will not block the production of sympathin by nerve impulses. This fact could be accounted for on Parker's view by assuming that ergotamine prevents the passage of adrenin into the responsive cell; it could equally well be explained on Elliott's view by assuming that it prevents the action of adrenin or the locally liberated sympathin on the contractile structure inside the cellular organization. For the present we must leave this difference of view unsettled.

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ENDOCRINE STUDIES
XXXVI. THE LEVEL OF OVARIAN FUNCTION DURING PREGNANCY*

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During the course of a long series of investigations on the disorders of the endocrine glands, preliminary report of which has already appeared in the literature (1), a number of individual patients were referred who presented amenorrhoea as a chief or subsidiary complaint. Each patient received a very thorough clinical and laboratory diagnostic study, the details of which are given in the above-mentioned publication. Experience early indicated that a certain number of this amenorrhoeic group gave function patterns consistent with "ovarian failure" and, equally, suggested an early pregnancy. A brief lapse of time naturally permitted a resolution of the problem and in nearly half of these cases the patient was found to be pregnant, while in the remainder the alternative endocrine state was demonstrated. The close parallelism between the two conditions, in certain of the important metabolic levels, was highly suggestive, but at the time of first notice only incomplete and somewhat uncertain data were available indicating the influence of normal pregnancy on vital function level. An investigation in this field was begun by the author in 1920, and a summary of the completed work has recently appeared (2). This study has yielded a series of objective criteria for the metabolic levels in normal pregnancy directly comparable with those characterizing ovarian failure as drawn from the series to which reference was made above (1). The present paper embodies an analysis of these two sets of data with the design of evaluating the probable level of ovarian activity during gestation. References to this point in the literature are meager and, in the main, are no more than ex-cathedra statements of over- or under-activity without supporting documentation. The present study offers an initial attempt to resolve the question on the basis of objective evidence.

The composition of the two groups can be presented most compactly in tabular form.

TABLE I
COMPOSITION OF GROUPS

Group	*Number*	*Total*
Ovarian Failure:		
Functional	300	
Castrates	30	330
Pregnant:		
Experimental Series	77	
Controls	23	100

*Read before the Fifteenth Annual Meeting of the Society for the Study of Internal Secretions, Philadelphia, June 9, 1931.

A few words of explanation may be apposite. The functional ovarian failures are a recent consecutive series of cases drawn from the much larger group forming the basis of the endocrine studies. The 30 castrates were patients studied by the same methods and within the same time interval. They constitute the control fraction of the endocrine group. The "experimental series" of pregnant women were demonstrably normal patients studied completely at brief recurrent intervals throughout the later months of pregnancy. The average duration for the members of the series comprised the last four lunar months; a large part of the individual studies covered six months or more. The data of this group summarize considerably more than five hundred independent complete vital function studies. The control group is composed of patients who were fortuitously studied during pregnancy and found to be entirely normal according to the established criteria. An appreciable number of them were referred for symptoms which were traced to an unknown or unacknowledged pregnancy.

Of necessity, from the character of the study, the individual ages fall within four decades. An analysis of the distribution presents certain points of interest.

TABLE II

AGE DISTRIBUTION

Group	*Under 20*	*21-30*	*31-40*	*Over 40*
Hypogonad:				
Functional	15%	38%	22%	25%
Surgical	0	18%	15%	67%
Total	13.2%	35.6%	21.2%	30.0%
Pregnant:				
Experimental Series	53%	33%	14%	0
Controls	4%	44%	48%	4%
Total	42.0%	35.0%	22.0%	1.0%

While the largest single group of the ovarian failures falls in the third decade, one-half of them were studied between the ages of thirty and fifty years. The majority of the castrates had passed the fortieth birthday, conditions requiring such drastic manipulating being relatively infrequent in the earlier decades.

The pregnant group shows a decided shift toward the earlier years, a fact conditioned in largest measure by the source from whence the subjects came. Fifty-six of this group were patients in homes for unmarried mothers, a circumstance influencing greatly the age of the individual. The major portion of the controls were women between the ages of twenty and forty. Reverting to the experimental group, the data from them shows a complete concordance with those from an independent group of pregnant women studied in another connection and not reported here, and also with the present control group. At the time of initiation of this study it was planned to report the data independently for each sub-group of the two major divisions. With the completion of the tabular presentation it was found that such differences as occurred were too small to be significant. In the interest of simplicity and of conservation of space, the succeeding treat-

ment will deal solely with the combined data of each of the two major groups.

A few of the fundamental physical data are significant, and these have been collected in the next table.

TABLE III

PHYSICAL MEASUREMENTS

Datum	*Hypogonad*	*Pregnant*
Age (years)	35	24
Weight (kgm.)	60.8	61.9*
Pulse Rate	75	78
Respiration Rate	16	17
Temperature	98.1	98.1
Blood Pressure		
Systolic	111	108
Diastolic	69	66

*Twelve weeks ante-partum.

The difference in age has already been noted. Weight in the pregnant group is recorded twelve weeks before delivery, this being an approximate mid-point for the majority of the series. The weight increment during pregnancy is substantially linear, at least for the last six lunar months, and the coefficient for this group was +0.46 kilogram per week. The pregnant woman shows a characteristically more rapid pulse rate and this has also been found to express a tendency in the hypogonad cases. Low blood pressures characterize both. In ovarian failure in the earlier decades an even more marked degree of hypotension is to be anticipated. The present figure absorbs the influence of certain extraneous factors but is to be regarded as representative of the group as a whole.

Relative values frequently assume an import lacking in absolute records. Two such are given in Table IV.

TABLE IV

PHYSICAL COMPARISONS

Datum	*Hypogonad*	*Pregnant*
Weight, above prediction		
%	52	83
Average Amount	+22%	+18%*
Weight, below prediction		
%	48	17
Average Amount	−12%	−17%*
Net Average	+6%	+12%*
Lung Volume (Average)	−20%	−12%*

*Calculated 12 weeks ante-partum.

Using the Dreyer (3) female standard of prediction based upon sitting height, half of the ovarian failures and seven-eighths of the pregnant women are overweight. Further, they show approximately equivalent amounts if the convention of weight twelve weeks before be observed. The much smaller number of the underweight pregnant women show an average significantly below the ovarian group. The general disparity in the weight

comparisons might well be anticipated. In addition to the fat and protein storage by the mother in pregnancy, the parturient woman is carrying four kilograms or more (foetus, placenta and amniotic fluid) of extraneous material which she ejects during delivery. If correction be made for this contribution to the total weight, the high percentage of overweight in the pregnant group would be appreciably diminished. Equally, the underweight of the lesser moiety would be significantly more pronounced. Pregnancy is a transitory state and succeeded by massive readjustments. (In the present group the average loss three and one-half weeks after confinement was 8.9 kilograms.) Untreated ovarian failure is a progressive condition for which exists no provision for a like rapid change of physical status. Of the established endocrine glands, failure of which predisposes to obesity, the tendency is least marked with the ovary. The overweight of pregnancy must be regarded as partly intrinsic in a temporary storage in anticipation of subsequent needs and partly as artefactual in the contents of the uterus.

Lung volumes are predicted both by the Dreyer Female "B" standard based upon sitting height and the mean of the West (4) correlations with standing height and area. Observed values are compared with the mean of these two standards. Here again a moderate discrepancy is noted which would be even greater if the pregnant figure were taken from results just before delivery. As has been noted by several, the pregnant woman shows a steadily increasing lung capacity in spite of the developing anatomical impediment. The test is peculiarly susceptible to the degree of cooperation of the patient, and the characteristic personality pattern of the hypogonad precludes in many cases wholly reliable measurements of this quantity. The scatter in a series of measurements from an individual pregnant patient is greater for this than for any other laboratory measurement. The observed value reflects sharply the willingness of the patient to exert herself—and this is a highly variable factor.

The significant urine data are given in the next table.

TABLE V

URINE ANALYSIS

Datum	*Hypogonad*	*Pregnant*
Volume (c.c.)	1120	1610
Specific Gravity	1.019	1.017
Albumin (%)	28	29
Casts (%)	20	11
Sugar (%)	23	34
P. S. P. (2-hour Av.)	55%	59%

While large urine volumes are a usual record in supervised pregnancy, it is a great question whether this reflects some intrinsic influence of gravidity on the water metabolism or is no more than an expression of the reiterated instruction to drink plenty of water. My own observation of a group of cases not under pre-natal care inclines me toward the latter explanation. The occurrence of albuminuria is seemingly a parity. In the case of the pregnant woman there is certainly an orthostatic factor and the amounts

recorded in this series were never more than minimal tracts. It appears with a definite frequency in the ovarian group but here, too, only inconsiderable amounts are recorded. There is a definite suggestion of renal impairment in the greater incidence of casts in the cases of ovarian failure, particularly as practically half of the group were less than thirty years of age.

The values for glycosuria require more than passing comment. In the ovarian series, one in every four shows a slight glycosuria, while one in three of the pregnant women shows the same abnormality. With the latter group these are demonstrated glycosurias; lactose plays no part until a few days before delivery and this period was excluded from consideration (5). My figures far exceed the usual incidence recorded, but they derive from continuous studies and each glycosuric individual showed a number of collections which were sugar free. If only those cases be considered in which an appreciable number of positive urines were collected, the incidence falls to 18 per cent, a value still higher but in better accord with the reports of others, most of which derive from the examination of single collections. Glycosuria is a common finding in pregnancy; equally, it is an intermittent phenomenon. The question of diabetes does not enter here as all of these women had low normal blood sugars.

The protein metabolism in pregnancy is an extremely interesting subject but space does not permit of extended discussion here. The nitrogen partition in the urine reflects one phase of it, and the results of these analyses are collected in Table VI.

TABLE VI

NITROGEN PARTITION

Datum	*Hypogonad*	*Pregnant*
Total Nitrogen (gms.)	8.36	8.22
Urea " (%)	80.3	79.8
Uric Acid " (%)	2.1	2.7
Ammonia " (%)	4.0	4.9
Creatinin " (%)	4.6	4.7
Residual " (%)	9.0	7.9
% Residual over 9%	47	39

The somewhat low level of the total nitrogen in the pregnant group is explained, in part at least, by the nitrogen storage, both by mother and foetus, that characterizes the condition. Likewise, the slightly high value for uric acid elimination is a feature of pregnancy and the amount drops absolutely and relatively after the uterus is emptied. In the main, the partition formula is a fairly normal one, the upward tendency of the residual nitrogen being perhaps the most significant departure. This tendency on the part of the residual nitrogen becomes an established fact in the ovarian cases; the percentage with this component above the normal level (47 per cent), however, is not markedly greater than that of the pregnant group (39 per cent). It is a general indication of a disturbed metabolism and is common alike to all of the endocrinopathies and a wide scatter of non-

endocrine conditions. The difference in the two groups under consideration must be regarded as one of degree rather than of kind.

The blood chemistry shows certain striking differences as can be seen in the next table.

TABLE VII

BLOOD CHEMISTRY

Datum		*Hypogonad*	*Pregnant*
Non-Protein Nitrogen	(mgm.)	31	25
Urea Nitrogen	(mgm.)	14	12
Urea/Non-Protein	(%)	45	48
Uric Acid	(mgm.)	3.2	3.3
Creatinin	(mgm.)	1.5	1.5
Residual Nitrogen	(mgm.)	15.3	11.3
Sugar	(mgm.)	96	84

The lower non-protein and urea nitrogen values are a feature of pregnancy that has been frequently recognized. The uric acid values are both normal and substantially the same. The older Benedict-Franke (6) method has been used throughout for this analysis in order that all results might be mutually comparable. The blood sugars of the pregnant group are low normal, as was noted above. The gonad series yields normal data throughout; the pregnant group shows certain low nitrogen values seemingly reflecting the physiological condition since they rise to normal levels after delivery. The storage of protein which goes on through gestation introduces a special influence from which the members of the gonad series are free.

The blood morphology is also recognized to be greatly influenced by the pregnant state. The figures of the series are given in Table VIII.

TABLE VIII

BLOOD MORPHOLOGY

Datum	*Hypogonad*	*Pregnant*
Haemoglobin (%)	88	67
Erythrocytes (10^6)	4.81	4.15
Color Index	0.91	0.81
Leucocytes (10^3)	7.64	9.58
Polymorphonuclear Neutrophiles	57%	69%
Lymphocytes	35%	25%
Endothelial Leucocytes	6%	5%
Eosinophiles	2%	1%

The definite secondary anaemia of pregnancy finds no complement in the ovarian picture, nor does the established tendency toward increase of the neutrophilic fraction of the leucocytes. Seemingly, here, the mechanism influencing the blood morphology in pregnancy is one entirely apart from that operating in ovarian failure. In the latter condition, barring a tendency toward a relative lymphocytosis which is a common feature of all endocrine conditions—and many in which the ductless glands are not involved—the picture is a very normal one. One is constrained to connote a

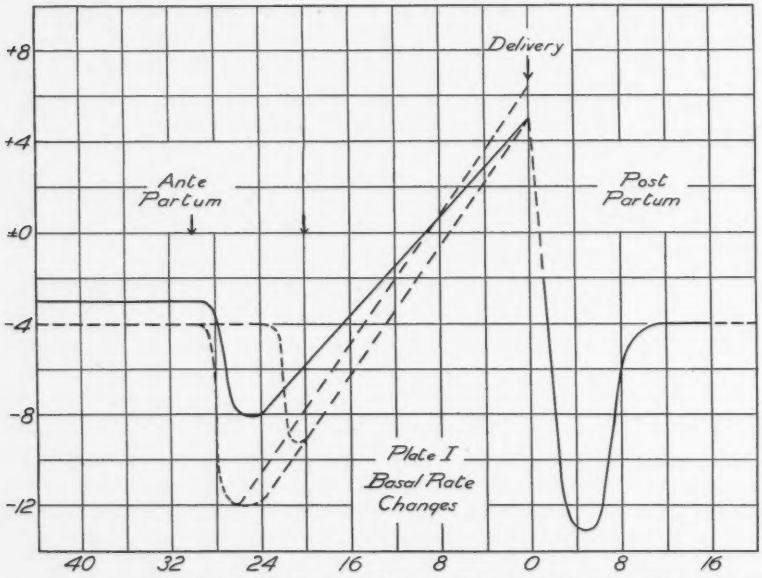
special group of agencies, intrinsic in the state of pregnancy, and operating to produce the characteristic blood picture.

The respiratory exchange as controlled by the energy requirement of the organism is a measurable end result and one profoundly influenced by a great variety of factors. Its expression as the basal metabolic rate is based upon elaborate studies of normal individuals and the correlation of their requirements with certain easily obtained biometric quantities such as age, height, and weight as in the Harris-Benedict prediction (7) or age and surface area as in the Aub-DuBois (8) standards. In these latter the surface area is derived by computation from height and weight, using the area formula of DuBois and DuBois (9). The usual practice is to define the basal rate in terms of per cent of variation from prediction, designating as normal those values which fall in the zone ± 10 per cent from the prediction curve. My own practice has been to compare the observed rate with the mean of the two prediction standards and regard $+15$ per cent and -10 per cent as the limits of the normal zone. All of the uncontrollable errors in the measurement tend to raise the observed rate; from this fact, -10 per cent is therefore more indicative of hypofunction than is $+15$ per cent of the converse.

The studies on the series of pregnant women showed a most interesting sequence of basal rate changes which can be shown most clearly by graphic presentation. (See Graph I, next page.)

The solid line represents the average of my own group of 77 women, while the dotted lines record observations of Boothby and Sandiford (10) and of Root and Root (11) on single cases. Obviously, in all of the cases, the basal rate remains at a normal level for a number of weeks after conception has taken place. There then follows a period of readjustment, during which the rate falls significantly, ultimately reaching a level tending toward, or indicating, hypofunction. Following this there is a progressive linear rise to a point somewhat above normal prediction immediately before delivery. In the Boothby case, the minimum falls somewhere between the thirtieth and twenty-sixth weeks, with Root and Root between the twenty-fourth and twentieth weeks ante-partum. In my own series, 14 of the patients were studied over periods permitting the determination of the position of this involution phase. They all fell between the thirtieth and twenty-second weeks ante-partum, with the majority centering about the twenty-fifth-twenty-sixth week interval. It will be noted that relative values are plotted, *i.e.*, the degree of departure from prediction. This permits the absorption of such variables as changing weight, which naturally affect the prediction standards. In my own series the studies were continued for some sixteen weeks after confinement and the characteristic course of the curve is given in the graph. After delivery there is a rapid falling off in the energy requirement which establishes a new low level at an interval of some four weeks; this is followed by a recovery almost as rapid, and in less than three months after parturition the oxygen consump-

tion is at the same normal level as that which characterized the early days of pregnancy. A reasonable interpretation of these data would be that early in pregnancy (from the middle of the third to that of the fourth lunar month) some factor interposes with sufficient effect to lower the energy requirement by an appreciable amount. Thereafter, a second series of opposing agents intervene—potentially the growing foetus as one only—and this gradually over-compensates for the first depressing influence, raising the oxygen requirement to a level above that initially recorded and actually above prediction. Parturition seemingly removes this second factor—hence, in part, the assumption of a possible foetal influence*—and there is a rapid decline to a level inferior to the previous low limit. Again, thereafter, there is a progressive and fairly rapid rise to the initial level. This



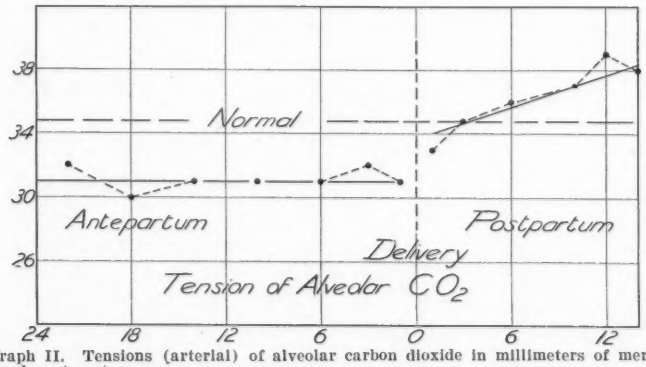
Graph I. Relative changes in the basal metabolic rate, both ante- and post-partum, showing zone of readjustment of gestating organism.

second drop in the basal rate could be interpreted as a reassertion of the first agent after the opposing factor had been removed by the termination of the pregnancy. Further, as the primary condition pregnancy, which called into being the first agent, has terminated, the influence of this latter gradually diminishes with restoration to normal levels.

Before discussing this matter further, consideration may be given to the respiratory exchange in ovarian failure. The average of the group of functional failures is —16 per cent below prediction, that of 30 castrates, —21 per cent. Scattered through the literature are occasional statements

*The whole question of foetal influence has been discussed elsewhere (12) and shown to be incompetent to account for the entire change.

that castration produces little or no change in the basal rate. Our own experience has been directly the opposite; an analysis of the factors involved may serve to resolve the apparent discrepancy. In estimating the so-called basal metabolic rate by measuring the oxygen consumption, convention has defined two limiting conditions, the strait observance of which is essential if representative results are to be obtained. The first of these, a post-absorptive condition, is readily obtained by abstention from all food for a period of fourteen hours or more before the test. The second, that of complete physical and mental relaxation, is difficult to secure in any but the trained subject and impossible in an appreciable percentage of those patients referred for metabolism study. The ovarian patient is notoriously an individual with pronounced nervous instability that prevents repose. Only by education through repeated tests may approximately accurate measurements finally be made. In the more incoercive members of the group, the establishment of a trend is the best that can be hoped for. In my own experience, it is a not uncommon happening for the patient, outwardly calm and controlled throughout the entire period of investigation, to show a final basal rate 20, 30 or even 40 per cent below the first adjustment measurement of the series. Another factor also comes into consideration, although data are not as yet available for complete documentation. In a group of measurements which we have been able to secure on recently castrated females it is seemingly evident that the basal rate does not decline immediately after operation. Ultimately the individuals reach the levels recorded above with depressions



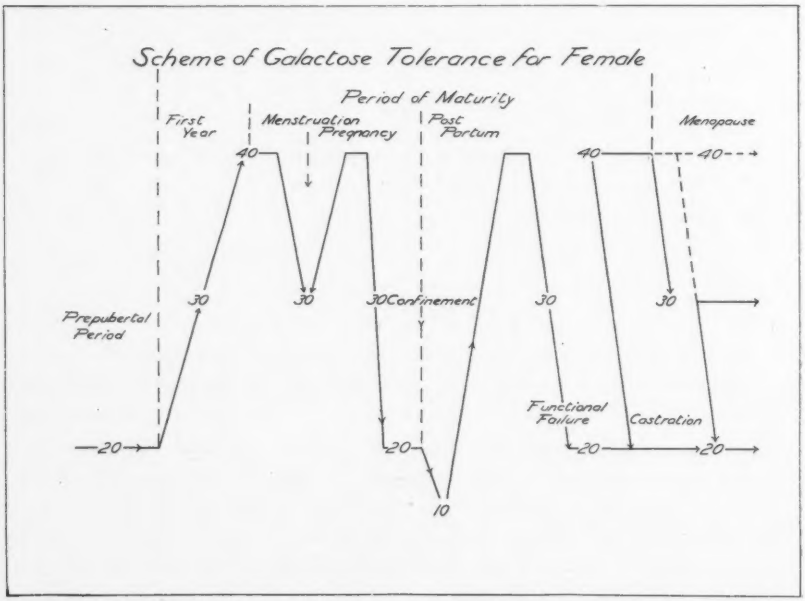
Graph II. Tensions (arterial) of alveolar carbon dioxide in millimeters of mercury both ante- and post-partum.

indicating a frank degree of hypofunction. It is, of course, possible that a true basality cannot be obtained with the patient recovering from the trauma of a surgical operation. Studies on this point are now under way, but the results are too few to warrant opinion. The point of interest to the present discussion is that both functional ovarian failure and castration in females produce a definite lowering of the energy exchange producing a moderate degree of hypofunction when compared with equivalent normal

individuals. To develop the present thesis, it may be argued that pregnancy produces a lowering of ovarian activity—using this term broadly; that other physiologic changes incident to the pregnancy compensate progressively this effect up to the time of delivery; that after delivery, the ovarian failure reasserts itself temporarily but that it spontaneously returns to normal levels, the causes initially producing it having terminated with the gestation.

Associated with the respiratory exchange is the tension of alveolar carbon dioxide, an index of the transport capacity of the blood for this product of catabolism. It is a well substantiated fact that normal pregnancy produces a lowering of carbon dioxide tension in those patients free from any evidence of acidosis. The results with the present series have been reduced to graphic form.

During pregnancy the modal level is 31 mm., a definite lowering from normal tensions. The corresponding figures for the other groups are : (a) control pregnant series, 31 mm.; (b) functional ovarian group, 35 mm., and (c) castrate group, 36 mm. The exact agreement of the pregnant control series is fortuitous; the depressing influence of them all is unmistakable. The like downward tendency, even though the degree be somewhat less, is definite in the ovarian group. The corresponding average value from a group of normal young women in a state of sexual rest was 43 mm. Further, in spite of low carbon dioxide tensions, the endocrine series gave no evidence of any acidotic condition.



Graph III. Diagram illustrating influences of age and sexual activity upon the galactose tolerance in the female.

Earlier in the paper the common finding of glycosuria in both the ovarian and pregnant series was noted. This indicates a disturbance in the carbohydrate metabolism with a presumptive lowering of the assimilation limit. In a series of previous papers on the metabolism of galactose (13) studies of the conditions now under consideration have been reported. The galactose tolerance of the female is seemingly much influenced by agencies associated with the ovarian and reproductive activities. The several relationships can be shown most compactly in diagrammatic form. (Page 490.)

The diagram indicates that during pregnancy there is a lowering of the galactose assimilation limit to the level characteristic of the prepuberal child; further, that ovarian failure and castration, the latter both before and after the menopause, produce a like result. The actual figures in the pregnant series are collected in tabular form. The post-partum data are included to show the slow but definite return to the normal adult level after the conclusion of the pregnancy.

TABLE IX

ANTE- AND POST-PARTUM CHANGES IN GALACTOSE TOLERANCE

Period	*Month*	*Tolerance Dose* *20 grams*	*30 grams*	*40 grams*
	3	67%	33%	0
	4	67%	33%	0
	5	63%	37%	0
Ante-partum	6	67%	33%	0
	7	62%	38%	0
	8	89%	11%	0
	9	100%	0	0
		Delivery		
	1*	100%	0	0
	2	73%	27%	0
	3	100%	0	0
Post-partum	4	67%	33%	0
	5	25%	75%	0
	6	0	50%	50%
	Over 6	0	0	100%

*3rd and 4th weeks only.

Mild ovarian failures produce a lowering to 30 grams (25 per cent), those more severe, to 20 grams (50 per cent). The 10-gram decrements are determined by the method of applying the test, those differences in the test meals having been found to give the most satisfactory and informative results. The average for the ovarian series which contained cases of various degrees of severity was —44 per cent, while for the castrates the value was —50 per cent.

Up to the present, consideration has been given solely to the findings resulting from objective methods of study. Recognizing the greater uncertainty of definition, particularly from the quantitative standpoint, it has none the less seemed interesting to consider a group of clinical reports usual in the two conditions. For ease in consideration, these are also collected in tabular form.

TABLE X

IMPORTANT CLINICAL FINDINGS

Datum	*Hypogonad*	*Pregnant*
General Gastro-intestinal Disturbance	30%	+
Nausea	28%	+
Vomiting	24%	+
Gastric Flatulency	25%	+
Constipation	40%	++
Nervous Instability	100%	++
Psycho-neuroses	32%	+
Personality Changes	very high	+
Tremors	+	+
Syncope	18%	+
Paraesthesias	17%	+
Fatigue	over 63%	++
Frequency of Urination	19%	+
Dyspnoea without Palpitation	over 40%	+
Pigmentation	+	+
Poor Teeth	58%	++
Thyroid Enlarged	33%	+
Visual Fields Contracted	over 40%	60%
Blind Spots Enlarged	+	+

The figures for the ovarian group are drawn directly from the clinical reports on the patients constituting this series. The pregnancy symptoms are matters of common report. The figure for contracted visual fields in this latter series is drawn from a group of measurements made with the Ferree-Rand perimeter and reported by Johns (14). It is interesting to note that these changes were not temporal cuttings, as have been reported by numerous observers, but were concentric contractions, the type of modification also reported in the ovarian series. In reviewing the several items in Table X it should be recognized that not one of the symptoms indicated is peculiar alone to these two conditions but all are end results of a wide variety of causes. The same comment applies with equal force to all of the material in the preceding tables of the more objective findings. In the coincidence and parallelism in so wide a range of evidences lies what significance there may be attached to this analysis.

Reverting to the table, but few, if any, of the items call for individual comment. Disturbances of the gastro-intestinal tract and of the stability of the nervous mechanism are common to both. Errors in calcium metabolism, as shown by poor teeth, and slight enlargements of the thyroid gland are more objective findings that are frequently recorded. The eye changes have already been noted. It may be added that the contracted fields of the pregnant group return to normal proportions after delivery.

DISCUSSION

Before undertaking any review of the foregoing material, one essential point must be emphasized. The case of ovarian failure presents an established state which may be progressive in severity but which is an entity producing characteristic changes in certain important function levels. Assuming for the moment that an analogous condition obtains in the pregnant woman, her physiological condition adds to the picture a large number of

other factors, some of which, at least, are entirely independent of the endocrine condition. Many aspects of the metabolism in pregnancy are concerned with the growth and nourishment of a rapidly growing mass of highly differentiated tissues which are superimposing their individual metabolic activities upon those of the mother. But we are able to measure the end results of these conjoint processes only through the final expression of the maternal organism. For these reasons it is hardly to be anticipated that the vital function pattern in the two conditions would exactly coincide. Only those important functions that work directly in control of the maternal activities can be expected to be equally affected, and even these may be confusingly influenced by superimposed effects of an origin extraneous to the common condition. A second difficulty arises in the interpretation of the term, ovarian failure. The numerous brilliant investigations of the past few years, far from bringing clarity to our conceptions, have but served to make confusion even "worse confounded." Advocates of the follicle, the corpus luteum, even of the interstitial cells, are all pressing the claims of these several entities with well documented investigative results. Further difficulties are engendered by the inclusion of other endocrine foci as active agents, the ovarian influence being assumed to be only indirect and operating through those other members of the endocrine concert. In the present instance, it has been possible to avoid, in largest measure, the existing confusion concerning the endocrine function of the several ovarian moieties by deriving the whole picture of ovarian failure from that produced by castration, a condition that will be conceded by all to present a true hypogonadism. The exocrine ovarian status throughout pregnancy is far from established. The corpus luteum seemingly inhibits ovulation during gestation, although in various animal species, removal of the corpus at a sufficiently advanced state of pregnancy permits of ovulation without terminating gestation. Results with animals, however, must be applied to human performance with the utmost caution, if at all—a rule far more honored in the breach than in the observance. After delivery, ovulation certainly takes place without menstruation, as the long tale of impregnations of amenorrhoeic, post-parturient women will amply testify. The recovery of the basal rate after delivery might be interpreted as a resumption of the follicular endocrine activity or, equally, a renewed function of the interstitial cells. The observations here reported are incompetent to resolve any of these questions. The only inference that seems warrantable is that in pregnancy and in ovarian failure certain vital function levels are modified in a very similar manner, both as to direction and amount. Hyperfunction of the ovaries, if there be such a condition, which, conservatively stated, is highly doubtful, should produce results the opposite of castration, causing an increased basal rate, a rising sugar tolerance, and so forth, all of which are the opposite of the actual observations.

In other words, there is a certain amount of evidence which is consistent with, though it does not define, a lowered level of ovarian endo-

crine activity during gestation. The close parallelism in the pictures produced alike by functional ovarian failure with amenorrhoea and early pregnancy is striking. It urges caution in the establishment of a diagnosis until sufficient time has elapsed to resolve the major question.

SUMMARY

A comparison has been made between a group of patients with ovarian failure, of whom 300 were functional and 30 surgical in origin, and a similar group of normal pregnant women, 77 of whom were studied at two-weeks' intervals for approximately the last six lunar months of pregnancy. To these were added 23 controls. A variety of biometric blood, urine, respiratory and carbohydrate metabolism observations are recorded and compared. In addition, a brief survey is made of the correlations of a long series of important clinical findings common to both conditions. It is concluded that there is a certain amount of evidence which is consistent with, though it does not define, a lowered level of ovarian endocrine activity during gestation. The weight of the objective evidence completely negatives an ovarian over-activity—if, indeed, there be such a condition. The close parallelism in the pictures produced alike by functional ovarian failure with amenorrhoea and early pregnancy is striking and urges caution in the establishment of a diagnosis until sufficient time has elapsed to resolve the major question.

The author wishes to express his thanks to the colleagues and associates who have made such significant contribution to this work. Also to the patients without whose cooperation the investigation could not have been made. Thanks are also rendered to the American Association for the Advancement of Science for a grant used in a portion of the study.

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SOME CLINICAL RESULTS FROM THE USE OF ADRENO-CORTICAL EXTRACT AS PREPARED BY THE METHOD OF SWINGLE AND PFIFFNER

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INTRODUCTION

In a series of recent articles, Swingle and Pfiffner (1, 2, 3, and 4) have published detailed directions for the preparation of a physiologically active extract from the cortical substance of beef adrenals.

They believe that this extract represents the active principle of the adrenal cortex. Support for their opinion has been furnished in tests conducted upon adrenalectomized cats. Some of these experimental animals were allowed to reach the comatose stage of adrenal insufficiency before treatment with the extract was begun. That this adreno-cortical extract does contain the vital principle of the adrenal glands is shown by the fact that injections of it not only revived these cats, but maintained them in apparently normal conditions of health and vitality over a period of 100 days. Careful search revealed no accessory cortical tissue. Cortical extracts used prior to this (5) (6) (6a) had not approximated the success of Swingle and Pfiffner's product, though they had shown considerable potency. Other investigators (7) (7a) (8) have also prepared extracts with similar properties.

Many early investigators have studied the clinical effects of desiccated adrenal gland substance and crude adrenal extracts in Addison's disease. Recently Stewart and Rogoff (9) and Hartman, Aaron and Culp (10) have reported the favorable treatment of this malady with cortical extracts. Because of a number of favorable clinical results (11) (12) (12a) (13) (14) reported from the use of Swingle and Pfiffner's preparation, we have adopted it for use in several cases that have come to our attention.

The primary purpose of this communication is to report the results from the use of this extract in the treatment of three cases of Addison's disease. In these cases every precaution was used to rule out a possible psychic factor, which too often casts its shadow over the scientific value of clinical data. Its secondary purpose is to suggest a wider clinical application for this extract, and to report its use in diseases which, unlike Addison's, are not medical curiosities.

We make the extract ourselves and the investigation is being conducted with the cooperation of three groups of physicians connected with the staff of the Colorado General Hospital. These men not only have been willing to cooperate, but their eagerness to apply this physiological

discovery to practical ends has been refreshing. We first produced the extract for a patient whose symptoms indicated a possible need for adreno-cortical therapy. Its use attracted some comment. Three cases of Addison's disease soon came to our attention, each accompanied by insistent requests for the cortical hormone. The results of these experiments are embodied in this paper.

The actual treatment of these cases has been chiefly in the hands of clinicians. Some time ago we asked these men to prepare their findings and conclusions for publication. Except for slight additions required to bring the protocols up to the date of submitting this for publication, they are in the original form. The protocol of case 2 has been taken from the files of the Out Patient Department at the Colorado General Hospital. In order to assure recognition to our co-workers, we have identified each case with the names of the physicians who administered the treatments.

We believe that the psychic element has been eliminated from this work. Conscious effort and the circumstances under which the work was conducted have been the two factors contributing to the achievement of this end. We submit our efforts in this direction for the scrutiny of those who may be inclined toward unusual skepticism where clinical data are concerned.

1. At least once during the course of treatment, an old impotent extract, or a diluted potent extract was used unknown to either the patient or the physician in charge of its administration. The patient invariably failed to respond to such injections.

2. These patients were not in the hospital, consequently they were free from the possible influence of others who might be under similar treatment. Not only was each case conducted independently, but a different group of physicians was in charge. These groups were not familiar with the results being obtained in other cases being treated. We are convinced that nothing short of actual results has influenced these men in forming their opinion.

PROTOCOLS

Case No. 1. (C. F. Kemper, M.D., and P. A. Dickman, M.D.)

"The patient when first seen on Nov. 26, 1928, was 21 years old and presented complaints of weakness, swelling of the ankles, amenorrhea, occasional attacks of vomiting, and cramping of hands. These symptoms were of six weeks duration. Examination revealed dry skin, enlargement of the liver, dependent edema, and a blood pressure of 100/80. From this time until December, 1930, she developed in succession nausea, vomiting, and diarrhea, marked vascular hypotension (blood pressures as low as 75/50) and extreme muscular asthenia, with well defined remissions and exacerbations (or "crises") during the course. At the latter time a brownish patch on the upper lip and spotty pigmentation over the face and neck were noted. A diffuse generalized pigmentation has since appeared over almost the entire body, but has never affected the mucous membranes accessible to examination. The syndrome above described constitutes the diagnostic picture of Addison's Disease.

"A modified Muirhead regime consisting of adrenalin by hypodermic injection and desiccated adrenal cortex by mouth was instituted in August of 1929 and was continued with benefit to the patient until December, 1930, when the adrenalin had to be discontinued because it apparently induced attacks of typical

tetany in dosage as low as one minim hypodermically. Since two blood calcium determinations were reported 4.5 mgm. and 6.9 mgm. per 100 cc., and since the spasm was relieved by the intravenous injection of calcium chloride, we concluded that it was due to hypocalcemia and so to hypoparathyroidism. The tetany is at present controlled by the administration of parathormone daily.

"During the month of January and the early part of February of this year her condition became so poor as to be considered almost hopeless. There was extreme dehydration from the repeated vomiting and incessant diarrhea, and a loss in weight from about ninety-seven to seventy-two pounds. Asthenia was so extreme that the patient could not turn over in bed unaided or even raise her hand without great effort. Early in February a marantic thrombosis of the left femoral vein developed which later involved the left external iliac vein since the cyanosis and edema extended to the left buttock and lower left abdominal wall; this complication responded quite promptly to the routine measures. Improvement in the general condition began during the latter half of February and continued gradually until March 5, when treatment with the cortical hormone made by Dr. Whitehead and Mr. Thompson according to Swingle and Pfiffner's technique was instituted. From the latter date until April 21 the extract was given in dosage of 1 to 5 cc. intramuscularly daily. On April 22, April 27, May 12, and again on May 26 the extract was given in 10 cc. doses intravenously without any untoward immediate reaction or any dramatic acceleration of improvement. The results of this treatment have been rather difficult to evaluate since the patient was already on the road to a remission before it was started. However, her condition has undergone a gradual, rather than a dramatically rapid, progressive improvement up to the present time (June 8, 1931). Vomiting has ceased and the appetite is now good; diarrhea is fairly well controlled with slight relapses; the blood pressure readings, in the order of their taking, have been 90/60, 100/70, and 105/60; her general strength has markedly increased so that for the past two months she has been able to walk about and be up most of the day; the gain in weight has been gradual from 72 pounds in February to 84 pounds in May; but the pigmentation has not changed appreciably. A scanty menstrual flow, which had been totally absent for 6-7 months previously, appeared in March. April and again more profusely in May. As intimated above, even intravenous injections of comparatively large doses of the extract have not produced any rapid change in the clinical picture, such as has been described by Rowntree and Greene in their work at the Mayo Clinic."

March 5, 1931, is given in the protocol as the date on which treatment with cortical extract was begun. Full strength extract was first administered on this date. A less active extract had been given in February. Its use was not beneficial but serves as a control over any possible psychic tendency on the part of the patient.

Slight relapses in the patient's diarrhea is also mentioned in the course of the protocol. These relapses came after we had given the physicians some extract that was too old to be potent. It had been kept in the refrigerator for six weeks without preservative. The diarrhea has been an outstanding symptom in this case. Its reappearance is a good indication that the patient's freedom from symptoms prior to the injection of impotent extract was due to nothing other than the effect of the potent extract. We know of no better control than the use of such an extract, unknown to either patient or physician.

The return of menstruation has never, to our knowledge, been effected in such cases by any other treatment.

This patient's liver was enlarged and extended two inches below its normal position in February. Dr. Dickman has very recently informed us that its size and position is normal. This improvement has taken place after only 3 months' treatment.

Inasmuch as we feel that it is logical to test the patient's reaction to the extract, our routine practice is to begin with the administration of small subcutaneous doses.

A daily dose of 2 cc. of cortical extract (by subcutaneous administration) was the original amount required for this patient. Intravenous injections of 10 cc. once each week proved equally effective. A saving of even 4 cc. of cortical extract is decidedly worth while. That the amount of cortical extract required by this patient recently has been decreased to a bi-weekly dose of 10 cc. is shown in the protocol. Desiccated cortex of the adrenal gland given by mouth may possibly account for this reduced extract requirement. This gland feeding was instituted as a final effort to conserve the extract. That this measure may be successful is indicated by the fact that this patient suffered no ill effects or exacerbations since the combined adrenal therapy was instituted.

Hewer (15) has claimed that the adrenal cortex is involved in calcium metabolism. Vincent and Thompson (16) suggest that the adrenal cortex and the parathyroids work together in regulating the blood calcium. Since the daily dosage of parathormone is being decreased in this patient, it will be interesting to determine if with continued adreno-cortical therapy, the use of parathormone can be completely eliminated.

Case No. 2. (Hobart A. Burch, M.D., Physician in charge of the Medicine Clinic, Out Patient Department, Colorado General Hospital.)

Case number 2830, male, aged 54 years, was a night watchman. He had been twice married. His parents had been long lived. He had had 7 brothers and 5 sisters. Five of the brothers were living and well, and 2 died of old age. Of the 5 sisters, 4 were living and well, and one had died of causes unknown to patient. He was born in Pennsylvania but had spent the last 35 years in Colorado. He had been foreman on municipal work up until the time of the present illness and had always worked overtime. The patient drank wine and beer when young and is a moderate user of tobacco.

He had had typhoid fever in 1910 with an uneventful recovery. In December, 1929, he had had mumps with testicular involvement. The present illness apparently dates from this time as he relates that his friends commented on his brown color on New Year's Day, 1930. He had felt weak since then and was forced to quit work on January 4, 1930. He said he was "too weak and dizzy" to continue as foreman. He was given the position as night watchman in the fall of 1930. There was a loss of memory, but no signs of nervousness.

Muscular asthenia resulting from this illness kept him in bed for 4 months following the first attack. He was admitted to the clinic on October 10, 1930. He complained of dyspnea, vertigo, nausea, asthenia, and had occasional non-radiating pain "like cramps" in right hypochondrial region. He was densely pigmented and emaciated. Pigmentation, while general, was most marked in exposed parts and in a belt around the abdomen.

The appetite was good but he complained of indigestion, gas formation, and occasional constipation.

The temperature ranged from 96.6° F. to 97° F. at various times.

The mouth showed pigmentation of mucous membranes. The teeth were poor.

There was no enlargement of the thyroid, and the cervical glands were non-palpable.

The chest was of the athletic type. Percussion and auscultation were normal over both lungs. There were no rales. The heart was normal. Blood pressure was 92/64 and the pulse 72. Heart sounds were muffled and distant, but there were no murmurs.

No evidence of calcification in the region of the suprarenal could be detected in a roentgenogram taken especially to investigate this possibility. Atrophy of the penis was noted. The gastro-intestinal series was negative. The liver was normal in size. Gastric analysis showed hypochlorhydria.

The erythrocyte count was 4,240,000 and the leukocyte 9,200. Differential blood count gave 51 per cent polymorphs, 45 per cent small lymphocytes and 4 per cent eosinophils.

The Wassermann test was negative.

The basal metabolic rate was ±0 (theoretical normal).

A diagnosis of Addison's disease was made.

The patient was treated and studied until December 22, 1930, the date of his last voluntary visit to the clinic. He had gained weight on a general tonic, and seemed stronger. He had also been taking an adrenal cortex mixture by mouth for some time and continued it until being called in on May 14, 1931, to receive treatment with the cortical extract.

On readmission to the clinic, May 14, 1931, he weighed 115 pounds and had been working regularly 3 nights a week. He was feeling fairly well, although his blood pressure was still 90/70. Blood and urine were obtained for study and he was then given 2 cc. of cortical hormone subcutaneously. Thirty minutes after injection he started to perspire and claimed to feel warm all over for the first time since becoming ill in January, 1930.

He returned to the clinic on May 18, 1931. The pain in the region of the right kidney had completely gone. Pigmentation was less in some areas. He felt stronger and was able to get in and out of his car alone, something unusual for him. He had not been troubled with vertigo since the first injection. A 10 cc. dose of the extract was given intravenously.

Three days later this patient received another 5 cc. of the extract intravenously. His temperature was higher than it had been in our previous observations, 97.9° F. His blood pressure was 92/72.

On May 25th he was given only 1 cc. of the extract. His blood pressure was 100/62. He was put on daily doses of 15 grs. of desiccated suprarenal gland.

He received from 3 to 4 cc. of the extract weekly. On June 4th he was feeling better, and mentioned that there had been a return of libido and that he had a night emission.

On June 8th this patient appeared to be in a worse condition than at the time of beginning treatments with cortical extract. His blood pressure was 70/50. This relapse may be due to an increased sensitivity to adrenal medullary secretion taken orally. He was in a more critical condition than at any time since he had been under our observation.

We feel that this patient was not at a critical point in the progress of the disease when cortical treatment was started. He was, however, gradually losing ground, his weight having dropped from 185 to 115 pounds. It had been many months since the onset of his affliction and there had been no indication of a turn in the direction of spontaneous recovery.*

Case No. 3. (T. D. Cunningham, M.D., and W. I. Covault, M.D.)

"Mrs. A. P., aged 48, American, female, housewife. The chief complaints were loss of strength and pigmentation of the skin. The present illness began in the latter part of February, 1928, when the patient noted beginning loss of strength and appetite. Having lost her husband during the same month, she considered her condition due to worry; she became progressively weaker and in two months noted irregular brownish spots on the back of her neck. These spots were about the size of a dime and quarter, respectively. By summer the patient began to become nauseated, especially in the morning, but by ten o'clock she was relieved. By fall all the symptoms were exaggerated and the backs of her hands and extensor surface of the forearm became involved in the pigmentation. There was an absence of libido. There was gradual loss of memory that became most marked in March, 1930. The appetite became progressively worse until she was forced to quit work in September, 1929.

"In March, 1929, the patient consulted a physician who pronounced her anemic and advised that all teeth be extracted. The extraction was done in April, with no benefit. About this time there developed a dull, aching pain in the epigastric region which was present at all hours and bore no relation to meals or soda. There were sharp pains in the shoulders, arms and hands. She was depressed mentally. Fats could not be tolerated, but there was a craving for citrous food.

"In February, 1930, the patient had an attack of bronchitis and was confined to bed for three days. After a week this cleared up but she still remained in a weakened condition.

*At present (Oct., 1931) he is showing steady improvement on cortical extract, having gained 8 pounds in weight the past 2 months.

"In March, 1930, the patient became so weak that she was unable to walk or sit up for any length of time in bed; the vision was poor and there was mental apathy as well as asthenia. Food and liquids were vomited and there was nothing retained in the stomach for a period of four days. She was seen at this time by Dr. T. D. Cunningham, who made the diagnosis of Addison's disease. She was taken to a hospital where she remained for three weeks.

"During hospitalization the patient was given fluids subcutaneously and rectally. Until the last week of hospital stay she was unable to retain anything but a slight amount of fluid by mouth. Adrenalin was administered in 5 minim doses daily; this was continued until April 28, 1931.

"A physical examination at this time showed a well developed and fairly well nourished woman very weak and apathetic. There was a brownish pigmentation over the entire face, forehead, backs of hands, extensor surface of the forearms, areolae of the breasts and the linea alba. On the mucous membrane of the mouth, just inside the angles, were patches of brownish pigment. The lungs were normal to auscultation and percussion; the heart sounds were distant, but there were no murmurs, thrills or arythmia. The blood pressure was 96 systolic and 80 diastolic. The rate was 72. Temperature was subnormal. There was tenderness to deep palpation in the epigastric region, not limited to any particular spot. The abdomen was otherwise negative. The genitals were normal externally. The reflexes were normal.

"*Past History.* She had had pneumonia at 5, tonsilitis at 16 and whooping cough at the age of 26. The whooping cough occurred in the fall and the following winter the patient developed a cough and lost 30 pounds. This weight was gained back in the next year. In 1914, a cyst was removed from the right breast. There were no severe injuries.

"*Personal History.* The patient was married at 19. The husband was well and died as a result of an accident in 1910. She was married again at the age of 41; the second husband died of chronic nephritis in 1928. The menses began at 14 and were regular every 28 days with moderate amount of flow of three to four days' duration; there was some dysmenorrhea before the birth of the only child in 1903. There was no evidence of a beginning menopause at this time. There was no history of a venereal infection, and the Wassermann test was negative.

"*Family History.* The mother died at the age of 67 of pneumonia. The father died of 'pleural pneumonia' at 57. There was one sister, aged 37, living and well. There were 2 brothers, aged 35 and 50, living and well. The patient stated that there was no tuberculosis in the family. Two maternal aunts died of cancer. The maternal grandfather died of Bright's Disease. There were no other familial diseases.

"On April 29, 1930, the patient was given 1 cc. of suprarenal extract, subcutaneously. In twenty minutes she noted that her 'legs felt lighter,' and in a half hour the peculiar sense of stomach consciousness left her. She also stated that her feeling of drowsiness was not quite so marked. She received injections of 1 cc. daily and in six days she resumed her domestic duties. In the meantime she continued to feel better and stronger. The drowsiness disappeared and she became 'anxious to keep busy.' Since going back to her work she had no recurrences of pains in any part of her body. Her strength has improved until she can climb three flights of stairs without difficulty. The mental depression has also cleared. About the tenth day after she began the treatment she became slightly nauseated after a meal of hot cakes, but has had no nausea since. The pigmentation is gradually fading, most notably on the terminal phalanges of the fingers and the areolae. The temperature was 99° F.

"Roentgenograms show that this patient had had in the past, some pulmonary tuberculosis. There was calcification in the region corresponding to the position of the suprarenals. This was more pronounced on the right side. The feeding of desiccated adrenal gland substance failed to cause any decreased need for the cortical injections. She relapsed, without her regular dosage, but tended to regain her strength within twenty minutes after an injection. Whether the lesions in her glands are active or not can possibly be determined by the course of the disease and the amount of extract required to maintain her in the present condition of health and vigor."

OBSERVATIONS ON DISEASES OTHER THAN ADDISON'S

The three cases of Addison's disease described in the preceding protocols have been studied to determine the effectiveness of Swingle and Pfiff-

ner's extract in hypoadrenia that is not greatly complicated by any infectious process. It has seemed to us, however, that some other diseases offer a degree of suprarenal cortical insufficiency, which, while not so marked as in Addison's is equally worthy of study with this extract.

Pulmonary tuberculosis is the first disease of this description to which we have given our attention. Many clinical men have expressed the opinion that a suprarenal insufficiency might be involved at least in the final stages of this disease. Approximately 80 per cent of Addison's disease is due to tuberculosis of the suprarenal glands. While these glands are not always infected in cases of pulmonary tuberculosis, we consider that the toxic action of the disease may overstimulate or otherwise impair the normal function of these glands. It was with this in mind that one of us (17) studied creatinuria in tuberculous men—thinking that the degree of creatinuria might be a measure of the extent of endocrine disturbance. This work is still incomplete, but the study is being continued.

Each of the three cases of pulmonary tuberculosis which we have studied represents a different stage in the progress of the disease. The need for complete histories of these cases is not sufficient to warrant quoting them at this time. A general statement concerning the experimental observations would, however, seem to be desirable.

None of these patients was in a serious condition from pulmonary tuberculosis when treatment was started. One was quiescent and the other two were mildly active. They were all of long standing, and gave every appearance of a need for adreno-cortical support. The most severe case presented many manifestations of Addison's disease.

Subcutaneous injections of small doses of the hormone produced immediate general improvement, but its tendency to aggravate the tuberculous condition makes its use hazardous. Conservative doses of 1 cc. are sufficient to increase the fever of some of these patients. Our observations indicate that large intravenous doses are to be used with caution.

One case of arthritis deformans has apparently made marked improvement in a relatively short time. The patient suffers much less pain and there is greater mobility of the joints.

DISCUSSION

The success attending the substitution of injections of this extract for the active glands in adrenalectomized animals (3) (18) is sufficient evidence that it contains that element of the suprarenals which is essential to life. Further work to sustain this fact would seem superfluous. Since, however, there is some question as to whether or not Addison's disease is the result of an uncomplicated adreno-cortical deficiency, we feel that every available clinical case deserves study. Furthermore, this study must extend over a long period of time before any definite conclusions can be drawn. The findings which we have presented in our cases are only the first chapter in a story which will be incomplete until the autopsy.

The indications are that this treatment of Addison's disease is efficacious. However, in evaluating favorable data on Addison's disease one must take into consideration the fact that spontaneous remissions are characteristic of this malady. The literature is full of "cures" which have been effected by various therapeutic agencies. Many of these patients eventually died of exacerbations of the ailment or of an infectious process apparently resulting from weakened resistance. Some of the early cures, however, may be traced directly to faulty diagnosis or spontaneous recovery. While we feel that none of our results can be attributed to such causes, review of previous clinical experience makes caution appear advisable at this stage of our work.

Kinnicut (19), Johnston (20), and Adams (21) give reviews of the clinical data available during the period of early attempts at organotherapy in Addison's disease. Perusal of these data convinces one that in less severe cases temporary improvement has at times been derived from the ingestion of desiccated or raw adrenal glands and from the subcutaneous injection of crude extracts of the whole gland. Comparison of results before and after the era of organotherapy would indicate as much.

In Adams' case, although desiccated suprarenal was given by mouth, bed rest was plainly a most helpful adjuvant. Many of these early "cures" were of short duration; incomplete records are available for others. Extracts used were of the whole gland. Either alcohol, glycerine or water was the solvent generally used. The most apparent success was obtained with the alcoholic extract. Since the most effective of modern extracts of known derivation are taken either from the crude alcoholic (3) (8), ethereal (7) or the aqueous (22) extracts of the adrenal gland, it is possible that some of these earlier extracts might have possessed some activity. Most of the adrenalin and a portion of the cortical hormone were extracted. The latter was probably destroyed by sterilization.

Our own observations give us little reason to doubt the efficacy of Swingle and Pfiffner's extract in the treatment of Addison's disease. The very nature of the disease, however, enjoins caution in the interpretation of clinical results with any form of therapy.

We present a review of several "cures" from the early literature to justify our hesitancy in this regard. These cases have been selected to illustrate various possibilities of error which are present in clinical observations and which are as pertinent now as when the cases were first described.

1. E. Lloyd Jones (23) in 1897 reported a case of Addison's disease. The patient was given desiccated whole suprarenal gland substance. Within a month after beginning treatment she was vastly improved, even to the extent of being less pigmented. This case was considered a most remarkable cure. In a personal communication, which Adams included in his review, Dr. Jones admitted an error of diagnosis in this case. The patient had died of pernicious anemia.

2. Byron Bramwell (24) reported another case in 1897. He wrote, "The patient was kept in bed for three weeks, and twice a week I injected with every care and precaution 15 minims of the sterilized suprarenal capsule juice." He later gave this "juice" by mouth every other day. The directions for preparing his alcoholic extract indicate that it was weak. Nevertheless the patient became much stronger, so much so that he walked 8 miles shortly before his death from "influenza." Autopsy revealed total absence of the "capsules" of the suprarenal glands. It is evident that bed rest and the extract, particularly the latter, benefited this patient for a time. But it was insufficient to maintain the patient indefinitely, particularly under the strain of excessive exertion and infectious processes.

3. C. G. Stockton's (25) patient ingested from two to three raw adrenals of sheep daily in sandwiches. Marked improvement was noted and Stockton wrote, "It is my judgment that improvement has been wrought mostly by eating of adrenals from sheep." In a later personal communication to Adams, he stated that the malady had followed its usual fatal course after a year.

Both Bramwell's and Stockton's cases represent examples of apparently true Addison's disease in which spontaneous remission, prolonged possibly by suprarenal organotherapy, temporarily postponed the fatal outcome. Before treatment with Swingle and Pfiffner's extract was instituted, the patients, whose cases were presented by Drs. Kemper and Dickman, and by Drs. Cunningham and Covault, had received adrenalin injections. One had ingested desiccated cortical substance as well. We do not know whether our treatment merely prevented an imminent exacerbation or did in fact cheat the malady of its fatal termination. Circumstances indicate the latter possibility is the more probable explanation. Both these patients appeared to be in a serious condition when the cortical treatment was instituted. They are vastly improved over the conditions obtaining prior to the onset of the crises that caused them to seek medical attention. Only after they maintain this improvement for a considerable period of time will it be possible to accurately judge the effectiveness of the extract.

Three other cases are cited as examples of spontaneous and permanent remission of a group of symptoms which simulated the true Addison's syndrome. It seems possible that hypoadrenia in all of these cases may be attributed to temporary causes. Certainly no continuous pathological condition was involved.

4. Addison (26) in 1849, mentioned a hopeless case which was ostensibly cured by imbibing large quantities of brandy.

5. Adams (21) reports an interesting case of Fränkel's in this manner: "In our list, Fränkel's case (No. 35) furnishes a good example of the fallacies which may surround an observation. Here the result of the suprarenal feeding was *nil*, yet on inquiry three and a quarter years after the patient's discharge from the *Klinik*, he was reported quite well and

vigorous. Had this improvement begun while under treatment, the case could scarcely have escaped being regarded as an instance of permanent improvement from organotherapy."

6. George Oliver (27) first described a case in 1895, which was improved by use of alcoholic extract of suprarenal glands. After eight years this patient was still doing well with an occasional injection of the extract, which must have contained little more than adrenalin. Such success did not attend all of his attempts to apply organotherapeutic measures. He ascribed certain failures to the fact "that a very large number of the cases depend on tuberculization."

That Oliver understood the circumstances of his "cure" is indicated when he writes, "It is, however, not improbable that now and then cases may be met with in which the function of the adrenal glands may become lowered by some temporary cause, or may become impaired or crippled by a pathological state which has ceased to advance, or which may advance but slowly, and the influence of which only becomes more particularly apparent when the general health fails, from whatever cause. Then it may be that the suprarenal material introduced by stomachal ingestion will provide physiological aid of prime importance by merely supplementing the diminished autogenic supply."

Similar cases might be cited from the literature along with many more examples of failure of the organotherapy employed at that time. It is possible that an extract which successfully maintains adrenalectomized cats may prove inadequate in men with diseased or abnormally functioning suprarenals. Inasmuch as pathological processes in other organs may have developed simultaneously or in consequence of the adrenal cortical destruction, the conditions are not identical.

Simpson (13) reports the use of Swingle and Pfiffner's extract in a case of Addison's disease. He finds that the ingestion of desiccated adrenal substance maintains his patient after the cortical extract has brought her out of her critical stage of the malady. It would seem that desiccated gland is a much more effective adjuvant in the treatment of some cases than it is in others. We do not know what circumstances make this possible. It is true, however, that suprarenal ingestion has not as yet been able completely to replace the regular injections of suprarenal extract in any case with which we have had personal experience. We do not deny that such cases as Simpson's exist, but we believe that they are exceptions.

It is evident that the adrenal cortex is essential to the maintenance of life; but we doubt that the cortical extract alone will suffice to restore a normal status in certain cases of Addison's disease.

In one of our tuberculous cases, not an advanced Addisonian, thyroid feeding and occasionally additions of pancreatin and desiccated spleen substance seem to augment the effectiveness of this cortical extract. In a case of Addison's disease the use of parathormone was found to be necessary. We have been conducting some investigations which would seem

to indicate that the thyroid acts in conjunction with the suprarenal cortex to produce certain of its metabolic effects. Others have obtained results which indicate an interaction of the thyroid and adrenals.

In a recent preliminary report, Swingle, Pfiffner and Webster (28) present some metabolic studies along with a prediction of a possible thyroid involvement.

Our observations on pulmonary tuberculosis indicates that the extract improves the general condition where there is quiescence or slight activity. As yet our observations are too incomplete to make further statements possible, but we contemplate extensive investigation of adreno-cortical therapy in this disease.

Studies on Addison's disease should be invaluable in the investigation of the physiology of the suprarenal gland. Several other more prevalent maladies, however, afford promising possibilities for determining the practical usefulness of cortical extracts.

SUMMARY

The adreno-cortical extract of Swingle and Pfiffner has been made according to their directions and tested clinically on seven patients. Three of these patients had Addison's disease; three had pulmonary tuberculosis with varying degrees of hypoadrenia; one was suffering from arthritis deformans.

Precautions were taken to rule out any possible psychic factor in the clinical observations.

Favorable results are being obtained with all three cases of Addison's disease. The improvement observed is thought to be the result of treatment. Instances of remission and spontaneous recovery in earlier cases are cited to show that the very nature of the disease is such as to make positive conclusions impossible at present.

Experience with tuberculous patients shows that the use of this extract is beneficial in improving the general condition, but is possibly hazardous from the standpoint of the infection itself. The greatest danger seems to lie in administering excessive dosage intravenously, and in giving the extract to patients with active tuberculosis which may be aggravated thereby.

One patient with arthritis has experienced no ill effects from small subcutaneous injections. Pain has been relieved in the inflamed joints and mobility has been re-established in some of those that have been immovable.

Small subcutaneous injections of the extract are advised at the beginning of treatment. Some patients appear to be intolerant to desiccated whole adrenal gland given orally. Greater clinical benefit can at times be obtained by combining cortical administration with other glandular therapy for which the case may indicate a need.

ADDENDUM

Since this paper was written, several abstracts of papers read before the meeting of the Association of American Physicians, and dealing with this extract have made their appearance (29), (30), (31). The large intravenous dosage

used by Rowntree and Greene is striking in comparison with the small amounts required to obtain favorable results in our cases. Our belief that death may occur in Addisonians, even though they are treated with this extract, is substantiated by the observations recorded in these papers.

The authors wish to express their deep appreciation to Dr. Ivan E. Wallin for his assistance in revising the manuscript, and to Drs. Kemper, Dickman, Cunningham, Covault and Burch for their valuable observations and cooperation which made this report possible.

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PANCREATITIS AND DIABETES MELLITUS

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The cause of diabetes mellitus is not known and the pathology is not distinctive. The pathological physiology, however, is fairly well understood. The seat of the pathological process is generally believed to be the pancreas. A working etiological concept may be stated as follows: There is an hereditary stamp of normal functional longevity on each pancreas; in many people there is an hereditary weakness, a diabetic anlage as it were, that manifests itself as a result of some severe physical, mental or emotional strain or as a result of some disturbance in the normal endocrine balance as in the case of acromegaly, hyperthyroidism, pregnancy, the menopause, or obesity. Whatever the mechanism may be there seems to develop a functional deficiency of the islands of Langerhans. Excessive stimulation of insulin production caused by constant and prolonged ingestion of starches and sugars which usually results in overweight seems theoretically at least to be a reasonable cause for a functional breakdown on the part of the islands of Langerhans. A history of antecedent obesity is such a usual observation that overweight has become to be considered as the "first stage" of diabetes.

A history of an antecedent attack or attacks of pancreatitis would best establish the etiology of diabetes. Whether there occur clinically unrecognizable attacks of pancreatitis or not, it is singularly uncommon to elicit a history of a pancreatitis in a diabetic patient. The observation of a proved case of pancreatitis in a patient with a diabetic heritage, in which a diabetic state resulted, would tend to strengthen the hereditary concept of diabetes as well as establish the pancreas as the controlling organ in this condition. It is just such a unique combination of conditions that I wish to report.

B. J. N. A practicing dentist, Jew, aged 48, presented himself on March 8, 1931, complaining of tiring easily, frequency of urination, loss of weight, slight discomfort in extreme epigastrium or lower end of the sternum, lower right mid-axillary line, and an occasional tinge of nausea.

The onset of these symptoms was indefinite, beginning first with the mild lower sub-sternal discomfort associated with a little gas and a slight sensation of nausea. He next noticed that he tired easily. He consulted a physician at this time and was told that he had some liver disturbance for which he was given a laxative. His condition did not improve. He next noted an unusual thirst and a frequency of urination. A urine examination at this time showed considerable sugar. It was at this time that I saw the patient, three weeks after the onset of the above symptoms.

The patient's past history was essentially negative. He had had the usual childhood diseases and the "flu" in 1918 and 1927. His habits were regular. He was a moderate eater but favored breads and certain sweets.

His family history is of especial interest. His father died with nephritis and diabetes. His mother likewise died with diabetes. His only sibling, a brother, died with diabetes. Because of the familial incidence of diabetes, the

patient had always feared that he, too, might develop the trouble. Consequently, he had had his urine examined about four times a year. All examinations were negative up to the time the analysis mentioned above revealed sugar.

Physically, the patient was essentially normal. He measured 65 inches in height and weighed 165 pounds. His greatest weight was 180 pounds, average weight 170 pounds. His tonsils were present and cryptic. His abdomen was slightly distended but no definite tender areas were noted. Prostate examination was negative. His reflexes were normal. His blood pressure was 110/70, temperature 98.6, and pulse 80. There was present a slight icteroid tint to the sclera at the time he was first seen.

His urine contained 2 per cent sugar (single specimen). His blood count was practically normal except for 14 per cent large mononuclear leucocytes. The blood urea nitrogen was 13.4 and his fasting blood sugar 173 mgm. per 100 cc. of blood. Two hours following a breakfast rich in carbohydrates and sugars his blood sugar rose to 266 mgm. per 100 cc. A van den Bergh reaction was direct and there was 17.4 mgm. of bilirubin per 100 cc. of blood. At this time a tentative diagnosis of subacute pancreatitis was made and the patient was allowed to go to his home on a restricted carbohydrate diet. He was given directions to return for further study. He returned in one week. His jaundice was obviously more marked. The icterus index was 75 and the fasting blood sugar was 182 mgm. per 100 cc. of blood. An exploration was advised and Dr. W. E. Sistrunk operated upon the patient March 19, 1921. The pancreas was found to be diffusely hard, and there was considerable edema about the bile ducts and gall bladder. A cholecysto-jejunostomy was performed and a surgical diagnosis of subacute pancreatitis was made.

The post-operative course was uneventful. The clinical improvement was striking. On March 24, 5 days after the operation, the icteric index had dropped to 68. The patient was placed on insulin, 10 units every 8 hours, and his blood sugar varied from 100 to 152 mgm. per 100 cc. of blood for the first few days, but showed a distinct tendency to become lower as the jaundice disappeared. The icteric index dropped rapidly to 28 on March 28, and to 17 on March 30, and then fluctuated from 17 to 20 until the time of his discharge from the hospital on April 10. His insulin dosage was gradually decreased as his sugar tolerance improved until on April 7 it was entirely discontinued. At this time the patient was placed on practically a general diet, excepting gross sugars, and his fasting blood sugars ranged from 95 to 105 mgm. per 100 cc. of blood.

He has been seen twice since his discharge from the hospital. The first time was on May 1, 1931, at which time his icteric index was 16, his fasting blood sugar 111 mgm. per 100 cc. of blood. His color was good and he stated that he had been feeling fine. On the second observation, which was June 10, 1931, his fasting blood sugar was 95 mgm. per 100 cc. of blood and his icteric index was 12. The patient has gained his weight back to 165 pounds and states that he is feeling perfectly normal. He is still following a moderately restricted diet, avoiding gross sugars but taking three to four slices of bread daily, and all of the vegetables except the 15 to 20 per cent ones.

This case is remarkable in that it demonstrates the effect of a pancreatic disturbance in an individual who has a definite diabetic heritage. A frank diabetic state was produced which promptly disappeared following surgical relief of jaundice. Whatever the mechanism might have been, that is, whether the decrease in sugar tolerance was brought about as a result of disturbance in the liver cells and other tissues or whether it resulted from a pancreatic disturbance, it is apparent that the individual had a very narrow margin of reserve as regards his sugar metabolism, which is undoubtedly an hereditary manifestation. I have observed recently three other cases of pancreatitis, two subacute and one chronic, neither one of which has shown any evidence of disturbed sugar utilization, and one of these cases was in a Jewess. I think the frank implication here is that the patient would have developed a diabetes later on, possibly somewhere in the sixth decade, had he not become a victim of a pancreatitis when he did.

What the future has for this patient is a matter of speculation. It is my belief that he now has the best chance for avoiding a pancreatic breakdown since he realizes that his margin of safety is comparatively small. By careful dieting and protection of his pancreas, there is no reason to believe that he will later on develop a lessened sugar tolerance. Continued observation under careful control will reveal considerable information as regards his potential sugar tolerance.

SUMMARY

A case is reported of a moderately severe diabetes which developed in an individual who had a very strong diabetic background. The diabetes was undoubtedly precipitated by a subacute pancreatitis. Following surgical relief of the associated jaundice, the diabetes disappeared and the patient has what appears to be a fairly normal sugar tolerance.

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THE HYPOPHYSIS, CARBOHYDRATE METABOLISM AND DIABETES

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Our investigations (1924-1930) have shown us that the pituitary gland is one of the most important endocrine factors in the regulation of carbohydrate metabolism. This fact had remained unknown up to the present, but the significant frequency of glycosuria and diabetes in the course of acromegaly might have indicated its existence.

I. BASAL AND PROTEIN METABOLISM IN PITUITARY INSUFFICIENCY

According to Cushing and Davidoff (1927) in 66 per cent of cases with clinical pituitary insufficiency the basal metabolism is on an average 14 per cent below the normal standard; on the contrary in 46 per cent of cases of acromegaly the basal metabolism is increased to on an average +18 per cent. Hypophysectomy lowers the metabolism from +12 to —7 per cent. In hypophysectomized batrachians a decreased elimination of CO_2 has been reported (Winton and Hogben, 1923) but has not been confirmed (Putnam, Teel and Benedict, 1928; Houssay and Giusti, 1929). In rats extirpation of the pituitary decreases the metabolism considerably, 35 per cent, according to Foster and Smith (1926), to half the normal value (Putnam, 1929), and 40 per cent in our own observations.

Observations on the metabolism of hypophysectomized dogs have been made by Narbuta (1905), Wolf and Sachs (1910), Benedict and Homans (1912), Aschner and Porges (1912), Koster and Geesink (1929), Gaebler (1929), Artundo (1930). The state of the experimental animals or faulty technique invalidate these observations with the exceptions of Aschner and Porges' (1 dog), Benedict and Homans' (3 dogs), Gaebler's (1 dog), Artundo's (8 dogs). With the exception of Gaebler's paper the rest show a decrease. Artundo in our laboratory found that in 5 out of 8 dogs the metabolism was below normal, the maximum decrease being —30 per cent and the average —15 per cent (666 calories per day per square meter in hypophysectomized animals and 795 calories in controls).

Endogenous protein metabolism is diminished in hypophysectomized dogs. When on the same diet of meat as controls both experimental and normal animals eliminate the same amount of nitrogen, but during a 6- to 10-day fast, Braier in our laboratory has shown that 7 hypophysectomized dogs eliminated only 0.286 gm. per kgm. per day, while controls gave out 0.360 gm., i.e., 31 per cent more, a fact confirming Aschner's (1912) observation made on the fourth day of fasting. Hypophysectomized dogs that are receiving food eliminate less creatinin in urine (23 mgm. per kgm. per

day) than normal controls (28 mgm. per kgm. per day). Fasting experimental animals also eliminate less than fasting controls (experimental: 5.9 mgm. per kgm. per day; controls, 9.3 mgm. per kgm. per day). During phlorhizin diabetes hypophysectomized dogs eliminate less nitrogen than normal phlorizinised dogs (Houssay and Biasotti, 1930). (See table 2.)

Plaut (1922-23) first observed a decreased or totally absent specific dynamic action in hypopituitarism. Foster and Smith (1926) could obtain no increase in the respiratory exchange after injection of glycocoll in hypophysectomized rats; implantation of the pituitary restored the normal condition. Gaebler (1929) found a normal specific dynamic action in one hypophysectomized dog. Artundo (1930) in our laboratory observed that ingestion of 400 gm. meat produced in 6 hypophysectomized dogs the same increase in the respiratory exchange 5 hours after (398 calories per day per square meter) as it produced in 6 controls (396 calories per day per square meter), though in the operated animals the basal level was lower.

II. CARBOHYDRATE METABOLISM AFTER HYPOPHYSECTOMY

Glycemia. The blood sugar level of well-fed hypophysectomized dogs is the same as that of normal animals. After one day's fast there is no significant difference compared with the controls, but after several days without food the experimental animals had lower glycemia (0.076 per cent) than the controls (0.086 per cent).

Hypoglycemia in hypophysectomized dogs. Some animals show a tendency to have severe hypoglycemic crises that may be fatal. When the blood sugar level falls to and remains for some time at 0.07 per cent or below, symptoms appear; general weakness, postural instability, the animal falls and has difficulty in standing up again, there is abundant secretion of saliva, a tendency to opisthotonus, convulsions which may become violent, coma, the body temperature falls and death occurs, sometimes in a very few hours, at others after several hours. If sugar or glucose is given *per os* or glucose injected intravenously the animal rapidly recovers in some cases in 5 or 10 minutes, but in others it is necessary to repeat the dose. If the treatment is started only after the animal has had symptoms for several hours it is not always successful; indeed in a few of these cases intravenous injection of hypertonic solution of glucose hastened the death.

These hypoglycemic attacks were the cause of the loss of several hypophysectomized dogs which were otherwise in excellent condition. Such were No. 56, 23 days after operation, glycemia 0.06 per cent; No. 98, 28 days after, glycemia 0.05 per cent; No. 101, 40 days after, glycemia 0.07 per cent; No. 102, 68 days, glycemia 0.045 per cent, etc.

Hypoglycemia in hypophysectomized dogs may be considered according to the cause of onset as (a) spontaneous, (b) fasting, (c) phlorhizinic, (d) diabetic; (e) post-adrenalinic, (f) insulinic.

In fasting animals Braier observed hypoglycemic attacks in 4 out of 8 dogs (glycemias between 0.06 and 0.07 per cent), 6, 7, 9 and 12 days after beginning of fast; 3 of them died, one recovered after glucose was given; none of the controls died. The average glycemia during the fast was 0.08 per cent in the experimental and 0.097 per cent in the normal animals. On the last day of fasting it was 0.076 per cent and 0.086 per cent respectively. One hypophysectomized dog had severe symptoms with a blood sugar of 0.088 per cent, possibly due to alterations in the carbohydrate metabolism of the tissues.

Phlorhizin intoxication in fasting hypophysectomized dogs killed 15 out of 17 in 3 to 9 days, with typical hypoglycemic symptoms.

In 8 dogs of our hypophysectomized pancreatectomized series hypoglycemia occurred; 3 of them recovered after glucose treatment, one had 2 and another 3 hypoglycemic crises which were successfully treated.

In hypophysectomized dogs when adrenalin is injected on the fourth day of fast, after the rise of blood sugar hypoglycemia occurs which may produce coma. Glucose administration restores the animal.

Wilder (1930) has recently reported instances of severe hypoglycemia in cases of hypopituitarism with recovery when sugar was given.

Injection of insulin produces very severe symptoms and high mortality in hypophysectomized dogs (Houssay and Magenta, 1924, 1927, 1929). In hypophysectomized dogs hypoglycemia occurs more easily and is less well tolerated than in normal animals.

Tolerance to sugars. Cushing and his assistants have shown that after hypophysectomy in dogs it is necessary to give larger amounts of sugar *per os* to produce glycosuria. In numerous experiments, Houssay, Hug and Malamud (1921) observed this to be so only in some cases; what is more, continuous injections of glucose gave the same blood sugar curves in the experimental dogs as in the controls. Recently we have observed the blood sugar curve after injection of 1 gm. glucose per kgm. in dogs before and after hypophysectomy and found no difference between the two curves.

The respiratory quotient following ingestion of 50 gm. glucose was studied in 6 hypophysectomized and 4 normal dogs, increasing from 0.72 to 0.86 in the operated animals and from 0.74 to 0.85 in the controls. In both series the oxidation of glucose was therefore almost identical.

Sensitiveness to insulin. Houssay and Magenta (1924, 1927, 1929) have shown that hypophysectomized dogs are very sensitive to insulin. Injection of 0.5 to 1 unit per kgm., a dose that does not produce symptoms in normal animals (11 experiments) or those who have suffered a lesion of the *tuber cinereum* (5 experiments), is followed in hypophysectomized dogs by abundant secretion of saliva, convulsions, coma and death (8 out of 10 experiments). The blood sugar falls more rapidly to a level

somewhat lower and the normal level is recovered later in experimental animals. These results have been amply confirmed by Geiling, Campbell and Yshikawa (1927), Geiling and Britton (1927), etc., in dogs and by Houssay and Potick (1929) in toads. It has been maintained that in acromegaly there is an increased resistance to insulin (Davidoff and Cushing, 1927) but the statement is contested (See literature in Houssay 1929).

In toads extirpation of only the glandular lobe produces hypersensitiveness to insulin. In this species as in the dog extensive lesions in the *tuber cinereum* do not increase sensitiveness to insulin.

Antagonism between pituitary extracts and insulin. Since Burn (1923) published a paper on the subject numerous workers have seen that usually insulin is antagonistic to the pharmacological activities of posterior lobe extracts (See bibliographical summary by Houssay, 1929). Work has been done on (1) the antagonism between both substances; (2) action of pituitary extract on insulin secretion; (3) action of insulin on the structure and secretion of the pituitary; (4) hypersensitiveness to insulin in hypophysectomized animals; (5) modifications in structure of pancreas in hypophysectomized dogs; (6) pancreatic diabetes after hypophysectomy; (7) action of pituitary extract on diabetic hyperglycemia. A full report of all these subjects is made in the paper last mentioned; here only a few pertinent facts will be brought forward.

Up to now, in mammals, only posterior lobe extracts have the property of neutralizing the toxic effects and hypoglycemia produced by insulin. These extracts have a certain blood sugar raising activity. Anterior lobe extracts up to the present have never been active against insulin action. It is therefore natural that all authors have attributed exclusively to the posterior lobe any possible effect of the gland on carbohydrate metabolism. In our work, on the contrary, it is shown that the anterior lobe has a predominant, perhaps an exclusive role, in this respect. It is necessary, nevertheless, to demonstrate the existence of an active substance in the anterior lobe extracts of mammals.*

Posterior lobe extracts are antagonistic to the hypoglycemic and toxic action of insulin (Burn, 1923; Magenta and Biasotti, 1923; Joachimoglu and Metz, 1924; Moehlig and Ainslee, 1925; Voegtlin, Thompson and Dunn, 1925; Lawrence and Hewlett, 1925; Clark, 1926, etc.), also in hypophysectomized animals (Geiling, Campbell and Ysikawa, 1926; Geiling and Britton, 1927; Geiling, Britton and Calvery, 1929; Houssay and Potick, 1929). Houssay and Magenta (1929) have shown that the oxytocic principle has a more powerful action than the pressor principle.

Only in toads has it been possible to show clearly that implantation of the anterior lobe and injection of an alkaline extract of bovine anterior lobe has a definite activity against the effects of insulin (Houssay and Potick, 1929).

*The anterior lobe of the hypophysis of mammals (and man) increases diabetes in toads deprived of pancreas and pituitary.

III. DIABETES AND HYPOPHYSIS

Von Mering and Minkowski (1889) showed that extirpation of the pancreas produced diabetes. In 1922, Banting and Best in MacLeod's laboratory proved that diabetes may be controlled by the injection of pancreatic extracts from which, with Collip's assistance, insulin was afterwards separated. These facts, together with the observation of lesions of the pancreas in cases of diabetes, are the pillars on which the pancreatic theory of diabetes, today universally admitted, is founded. According to this theory the disease is always due to insufficiency of the endocrine function of the pancreas.

Pathological studies have shown the frequency of lesions in the islets (Opie, Weichselbaum, etc.), especially hydropic or hyaline degeneration or fibrosis. Nevertheless typical and constant lesions exclusively characteristic of diabetes have never been found, since those just mentioned may be observed in nearly one-half of the pancreases in cases in which there was no diabetes (Allen, 1922).

Diabetes and other glands. There are fatal cases of diabetes in which no typical lesions of the pancreas are found and in which the extraction of the gland shows the presence of insulin in amounts that would suffice to assure life for several weeks. This fact and others have been brought forward as proof that other endocrine organs play an important rôle in the production of diabetes. Hyperfunction of the thyroid or the adrenal medulla have been considered essential factors. Previous work in our laboratory has shown that pancreatic diabetes follows its usual course, with no alterations, in animals without adrenal medulla (Houssay and Lewis, 1921) or without the thyroid (Yriart, 1930). The part played by the pituitary is far more important, as will be seen after consideration of the following clinical and experimental evidence.

Diabetes in acromegaly. Loeb (1884), Pierre Marie (1886), etc., observed the occurrence of diabetes in some cases of acromegaly. In this disease glycosuria has been seen in more than 40 per cent of the cases (Borchardt, 63 out of 176; Rosenberg, 82 out of 196). Davidoff and Cushing found it in 25 per cent, but as it occurs at intervals they presume that continued observation would give a higher percentage of positive cases. Diabetes has been observed in 12 per cent (Hanseman, 1897; Davidoff and Cushing, 1927) to 35 per cent (Borchardt, 1908) of cases. It is often intermittent and has a non-progressive tendency. This frequent and significant coexistence of both diseases has always been considered a curious and unexplained fact.

Recently it has been suggested that in acromegaly there is a perturbed function of the vegetative nervous system centers in the diencephalon (Loeb, Erdheim, Leschke, Brugsch and Dresel, etc.). Leschke considers diabetes to be due to a primary alteration in nervous regulation of metabolic processes. His principal arguments are: (1) There is not always

the same degree of intensity in the pancreatic lesions and the diabetes. (2) The pancreas contains insulin sufficient to assure life during several weeks in subjects who have died in diabetic coma. (3) The regulation of the internal secretion of the pancreas can only be effected through the nervous system. (4) Psychic factors have marked influence on diabetes. (5) Lesions in the vicinity of the diencephalon (acromegaly) frequently produce diabetes. (6) Diabetes frequently coexists with obesity, polyuria and hypertension. (7) Diabetes is frequently associated with diseases producing polyuria.

The existence of insulin in an extract of pancreas does not signify that it was being secreted in sufficient amounts. The regulation of insulin secretion can be carried out almost perfectly by the denervated pancreas (Houssay, Lewis and Foglia, 1928-1929). Tumors and lesions of the diencephalon produce adiposity and genital atrophy and not diabetes. It has by no means been proved that diencephalic lesions are the only cause of obesity, polyuria and hypertension.

Several kinds of diencephalic lesions have been reported in cases of diabetes. (1) Cystoid cleavage between the *infundibulum* and the mid brain (Leschke); (2) lesions in the dorsal aspect of the *globus pallidus* (Dresen and Lewy); (3) in the *corpus striatum* involving the *nucleus caudatus;* (4) in the periventricular nucleus and the globus pallidus (Nicolescu and Raileanu); (5) in the *tuber cinereum* (Marinesco and Paulian). Lesions of the globus pallidus seen in Parkinson's disease do not usually produce diabetes (Nicolescu and Raileanu); in two cases of diabetes the paraventricular nucleus was found intact (Le Grand). No typical and constant diencephalic lesion can be described as characteristic of diabetes.

Davidoff and Cushing (1927) considering their clinical and anatomical observations believe that glycosuria in acromegaly is due to hyperfunction of the acidophile cells of the anterior lobe, associated or not with hyperfunction of the posterior lobe. In some acromegalic subjects no definite alterations in the pancreas are found. Partial extirpation of the adenomatous pituitary diminishes the hyperglycemia in some cases and increases the sensitiveness to insulin.

A lesion of the diencephalon might produce alterations in the functions of the pituitary, so that the diencephalic hypothesis does not necessarily exclude the pituitary.

Diabetes in other diseases of the pituitary. Glycosuria and diabetes are common in acromegaly, in which disease there is usually an acidophile adenoma of the pituitary. It would be interesting to know if in other diseases of the gland this is also the case. Colwell (1927) quotes a few cases, but Davidoff and Cushing in 168 observations of chromophobe tumors of the pituitary found glycosuria only in 4, and of these, 2 were later found to be acidophile tumors.

Experimental pituitary and diencephalic glycosuria. Extirpation of the pituitary sometimes produces slight glycosuria (Caselli, 1900; Gemelli,

1908; Goetsch, Cushing and Jacobson, 1911; Aschner, 1912; Houssay, 1916), that is also observed when the *tuber* is punctured without damaging the pituitary (Aschner, Leschke, etc.). Camus, Gournay and Le Grand (1923) performed a large number of experimental encephalic lesions in rabbits; in 9 glycosuria was observed, late in appearance, irregular and intermittent, prolonged and sometimes intense. They always found lesions of the paraventricular nucleus (which they call periventricular nucleus). Dewulf (1930) has also obtained similar glycosuria in 5 rabbits out of 58, but does not find lesions of this nucleus, only diffuse degeneration. It must be remarked that this author and those mentioned above occasionally observed spontaneous glycosuria in normal controls.

If these experiments could be given definite value they might serve as evidence of a possible diencephalic-pituitary glycosuria. It has been shown that the hypophysis receives nervous fibers from the supraoptic nuclei (Cajal, Vergara, Pines, Greving, Stengel). We have shown definitely that lesions of the tuber stimulate the melanophore expanding secretion (Houssay and Giusti, 1924; Houssay, Giusti and Goñalons, 1925; Schurmeyer, 1926) and the sexual stimulating secretion (Houssay and Giusti, 1929) and inhibits the diabetogenic secretion of the pituitary (Houssay and Biasotti, 1930).

Diabetes in hypophysectomized toads and in toads with lesions in the tuber or infundibulum. Houssay and Biasotti (1930, a) have shown that pancreatectomy produces an intense diabetes in toads at 20° C. with very marked glycosuria in 60 per cent to 100 per cent of the cases and hyperglycemia as high as 0.2 to 0.3 per cent. If the pituitary or only its glandular lobe is removed, pancreatectomy does not provoke glycosuria and the blood sugar increases slightly or not at all. If then an anterior lobe is implanted beneath the skin next day an intense diabetes with glycosuria and hyperglycemia is observed.

Lesions of the *tuber* prevent or hinder the appearance of pancreatic diabetes, but if a glandular lobe is implanted beneath the skin an intense diabetes develops. This diabetogenic activity of the implanted anterior lobe is not exercised through the diencephalon since hypophysectomized toads, with all of the brain removed forward of a section passing behind the *lobus infundibularis,* develop intense diabetes after pancreatectomy if an anterior lobe is implanted. All these facts can be interpreted as proving the inhibition of the anterior lobe by the diencephalon, an interesting incident of pituitary diencephalic association.

Pancreatic diabetes in hypophysectomized dogs. According to Goetsch, Cushing and Jacobson (1911), dogs with pituitary insufficiency tolerate better the effects on sugar metabolism of subtotal pancreatectomy. These results are not very convincing since in cases of subtotal pancreatectomy spontaneous recovery is always possible. Houssay and Biasotti's experiments (1930, b) of total pancreatectomy are free from this possible cause of error.

Hypophysectomy previous to or following pancreatectomy usually diminishes the severity of the diabetes. Survival may be as prolonged as 6 months, while pancreatectomized controls die in 1 to 4 weeks (See table 1). In dogs with lesions of the tuber made with a galvano-cautery and extending from behind the hypophysis to behind the mammilary bodies pancreatic diabetes has its usual development.

In hypophysectomized and pancreatectomized dogs the blood sugar was between 0.113 and 0.275 per cent; in the pancreatectomized controls it was from 0.3 to 0.35 per cent. Fasting produces marked lowering of the blood sugar in most hypophysectomized animals. It was observed that completely pancreatectomized dogs whose pituitaries had been removed sometimes had apparently spontaneous hypoglycemic attacks and sometimes died.

Glycosuria was not marked in these animals—between 0.05 and 0.89 gm. per kgm. per day (except in 2 cases out of 11)—while the pancreatectomized controls eliminated between 2 and 4 gm. per kgm. daily. It is also significant that fasting reduces or even completely suppresses this glycosuria even before the blood sugar is considerably reduced. Polyuria is only rarely observed after pancreatectomy in hypophysectomized dogs.

After giving sugar *per os* (100 gm. in 5 days) only 30 to 70 gm. were recovered in the urine. When 50 gm. were given sometimes none appeared in the urine, and never more than 56 per cent was recovered. In 5 pancreatectomized hypophysectomized dogs who had developed hypoglycemia 1 to 2 gm. glucose was injected intravenously and no glycosuria was subsequently observed.

The D:N ratio in the animals was always lower than in controls; therefore the carbon groups left after deamination can be metabolized in great part without being eliminated as glucose.

In 5 animals 8 experiments were made to test the influence of the ingestion of 50 gm. glucose on the R.Q. No. 81 (dog with hypoglycemia) showed an elevation from 0.71 to 0.84; No. 70 from 0.64 to 0.74; No. 97 from 0.66 to 0.75; No. 44 (after 2 days fast) from 0.69 to 0.81. In other cases the increase was less marked: In No. 70 from 0.67 to 0.7; in No. 93 from 0.71 to 0.75; in No. 44 no variation occurred. In several pancreatectomized controls the R.Q. was not altered by the ingestion of this dose of sugar.

In 4 hypophysectomized pancreatectomized dogs a low fasting R.Q. was found (0.64, 0.66, 0.66 and 0.67); the determinations were duplicated and found to be correct in all cases. These low R.Q., which would seem to indicate the formation of carbohydrate from fat, have not been observed by us in other cases.

Ingestion of sugar rapidly impairs the condition of these animals. Ketosis in moderate degree was found by Rietti by means of determinations made in urine by Van Slyke's method.

Phlorhizin diabetes in hypophysectomized dogs. Houssay and Biasotti (1930, c) have observed that extirpation of the pituitary renders dogs less resistant to injections of phlorizin after 3 to 5 days fasting. Six out of 8 died in hypoglycemia in 3 to 7 days. Controls and dogs with lesions in the tuber very rarely die under these conditions.

The elimination of nitrogen is high in the controls and low in the hypophysectomized animals (Table 2). The D:N ratio is also lower in the experimental animals. Their glycemia is lower and they eliminate only one-third of the sugar (calculated per kgm. per day), eliminated by the controls.

Diabetogenic action of extracts. Posterior lobe extracts produce hyperglycemia, but even repeating the injections it is impossible to produce diabetes by this means. No extract active for mammals has been prepared from the anterior lobe, up to the present, but eventually it may be possible to obtain the active principle and so have the final proof of a diabetes of hypophyseal origin. In hypophysectomized pancreatectomized toads subcutaneous implantation of the anterior lobe has an intense and specific diabetogenic action.

IV. MECHANISM OF ACTION

The principal arguments in favor of a predominant if not exclusive rôle played by the anterior lobe of the pituitary in carbohydrate metabolism are two: (1) Frequent occurrence of diabetes in acromegaly, in which disease there is an acidophile adenoma of the anterior lobe. (2) Implantation of the anterior lobe in the hypophysectomized toad protects against hypersensitiveness to insulin and reestablishes diabetes after pancreatectomy. The fact that in mammals implantation or injection of extracts have been unsuccessful prevents stating definite conclusions.

The fact that extracts of the posterior lobe produce hyperglycemia, and have an antagonistic action to insulin, indicates the possibility that this part of the gland plays a certain rôle. Implantation of posterior lobe in toads is less active than anterior lobe implantation in this respect.

The importance of the pituitary on carbohydrate metabolism is made clear by consideration of the following facts that have been discussed: (1) In hypophysectomized animals hypoglycemia occurs more readily and is less well tolerated, therefore there is greater sensitiveness to insulin, phlorhizin and fasting. (2) Pancreatic diabetes (dog and toad) and phlorhizin diabetes (dog) are much less severe. (3) Glycosuria is less marked after pancreatectomy or phlorhizin injection. (4) Sugar may be metabolized after pancreatectomy (increase in R.Q. and partial retention after sugar ingestion).

It is not yet possible to conclude whether in these cases there is greater consumption or less production of sugar. In favor of the first hypothesis it can be said that the R.Q. increases on sugar ingestion, a certain tolerance to sugar exists and the D:N ratio is low. On the other hand,

TABLE I

Nr.	Survival After Second Operation, Days	Weight, kgm.		AVERAGES							Interval Between Operations Days
		Initial	Final	Urine, cc. Per Day	Glucose Eliminated, gm. Per Day	Glucose Eliminated, gm. Per kgm. Per Day	N. Eliminated, gm. Per Day	N. Eliminated, gm. Per kgm. Per Day	D:N	Glycemia Average gm. %	
				Dogs Without Pituitary and Without Pancreas							
1	180	8.6	6.4	868	21.6	3.23	14.70	2.15	1.61	0.250	39
27	154	12.8	5.1	274	9.83	1.30	7.81	1.05	1.23	0.287	24
36	90	8.5	6.3	211	5.16	0.72	5.76	0.80	0.88	0.136	240
35	64	13.4	6.9	221	6.30	0.69	8.92	0.99	0.70	0.238	55
38	51	10.3	5.4	166	7.21	0.76	3.89	0.43	1.85	0.325	210
23	41	9.8	6.1	164	1.97	0.25	.....	.....	.....	0.267	27
11	35	12.4	10.2	356	0.688	0.059	.....	.....	.....	0.113	61
15	28	10.5	7.4	253	3.15	0.895	.....	.....	.....	0.218	41
29	25	10.0	6.1	160	4.42	0.552	.....	.....	.....	0.275	30
				Pancreatectomised Dogs With Lesion of the Tuber							
64	10	8.7	6.4	513	21.26	2.95	8.18	1.13	2.60	0.327	35
77	10	7.5	5.2	456	18.96	3.05	7.10	1.14	2.67	0.345	30
85	9	8.0	6.4	267	12.13	1.75	4.16	0.60	2.91	0.310	29
86	9	6.2	4.1	273	11.97	2.60	4.57	0.99	2.61	0.298	30
				Pancreatectomised and Thyroidectomised Dogs							
1	24	8.1	4.7	373	.....	3.18	.....	1.61	2.37	0.293	...
2	21	8.6	6.2	360	.....	3.10	.....	1.27	2.05	0.326	...
5	9	15.5	12.8	626	.....	2.55	.....	0.95	2.72	0.370	...
3	9	10.2	8.5	268	.....	1.47	.....	0.59	1.92	0.366	...
4	7	11.0	8.6	423	.....	2.15	.....	.....	.....	0.435	...
				Pancreatectomised Dogs							
..	7 to 30	up to 50% loss		500 to 2000	.....	2 to 4	.....	0.7 to 1.8	2.8	0.3 to 0.4	...

TABLE II

Average Variations Produced by Phlorhizin Diabetes in Fasting Dogs.

Days	Per Cent Loss of Weight			Glucose Eliminated in Urine gm. per Kgm. Per Day			N. Eliminated in Urine gm. Per Kgm. Per Day			D:N		
	Hypophysectomized	Controls	Lesion in Tuber	Hypophysectomised	Controls	Lesion in Tuber	Hypophysectomised	Controls	Lesion in Tuber	Hypophysectomised	Controls	Lesion in Tuber
Before Injection	..	..	..	....	....	....	0.99	0.93	0.97	....	....	....
1	1	2	3	0.60	0.97	0.81	0.62	0.44	0.57	1.41	1.99	3.54
2	3	6	6	0.68	1.29	1.55	0.62	0.69	0.79	1.81	2.35	3.29
3	5	7	9	0.78	1.99	1.75	0.37	0.71	0.78	1.67	2.88	3.03
4	10	14	13	0.41	1.94	1.41	0.21	0.65	0.54	1.69	3.05	3.17
5	12	17	16	0.81	2.91	....	0.35	0.91	0.69	....	3.21	....
6	12	21	..	0.76	2.49	....	0.25	0.64	....	....	3.29	....
7	..	..	..	0.42	2.82	....	....	0.63	....	....	2.94	....
..	..	..	..	....	2.66	....	....	....	....	....	....	....
..	..	..	..	....	1.96	....	....	....	....	....	....	....

against a high consumption of sugar we have the fact that the basal metabolism remains low, or increases only slightly, the basal R.Q. is 0.70, the elimination of nitrogen is also low, and the small amount of sugar eliminated by the urine, reasons all for supposing a smaller production of sugar. Perhaps both circumstances occur, lower production being the principal factor and also the cause of greater consumption.

The action of the pituitary may be direct on the tissues or indirect through the pancreas, liver or nervous system. An indirect action might be carried out by the regulation of the insulin secretion or the neutralization of its effects. The remarkable action of fasting on glycosuria and the attacks of hypoglycemia observed in hypophysectomized pancreatectomized dogs are not explained by this hypothesis. These observations can be understood if it is supposed that the anterior lobe hormone acts directly on the tissues, stimulating the production of sugar and perhaps retarding its consumption when insulin is lacking. It is interesting to correlate this hypothesis with the reduced endogenous protein metabolism observed in hypophysectomized dogs. It seems that the transformation of endogenous (or tissue) protein into sugar is reduced in hypopituitarism.

We believe that in the future the study of the influence of the pituitary on carbohydrate metabolism will reveal further information on their interrelation.

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COMPENSATORY HYPERTROPHY OF THE SUPRARENAL GLANDS IN THE RAT

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Compensatory hypertrophy of the remaining suprarenal gland after unilateral adrenalectomy has been noted by various investigators, but the amount and character of this hypertrophy are in several respects still somewhat uncertain. An experimental study of this question was therefore undertaken.

MATERIALS AND METHODS

In this study 24 young male rats of the Long-Evans hybrid strain were used from the colony in the Institute of Anatomy. The 24 rats included 12 pairs, with 12 controls and 12 adrenalectomized test rats. With one exception, the 2 rats of each pair were litter mates and as nearly alike as possible. Each pair was kept in the same cage throughout the experiment, except for 3 days after operation, when they have a tendency to attack each other.

These rats were all operated on at a weight of about 200 grams (average for test rats, 202 grams; controls, 203 grams), and at an average age of 66 days (range 60 to 77 days). That the suprarenal weights are definitely related to body weight is indicated by the study of Hammett (1) and others.

The right suprarenal gland was removed in the test rats under ether anesthesia through a lumbar incision. The control rats were also operated on; the right suprarenal gland was exposed but not disturbed. Recovery occurred within a few minutes after the anesthesia was discontinued and at no time after operation did the animals appear to be ill. In observing the effect of the operation on the general condition of the animal, weights were taken daily during the first week, then on the 9th, 11th and 14th days with weekly weights thereafter. The average weights of the test (adenalectomized) and control rats throughout the experiment are shown in figure 1. The suprarenal gland removed at operation was immediately placed in a moist jar and was weighed and preserved after the operation was completed.

These animals were kept on the standard diet (McCollum stock diet I) used in the colony. It consists of the following:

	Parts by weight
Casein (commercial)	15.0
Whole milk powder	10.0
Sodium chloride (table salt)	0.8
Calcium carbonate	1.5
Butter (unsalted)	5.2
Whole ground wheat	67.5
	100.0

The duration of the experiment ranged from 6 to 8 weeks, the average being 52 days in the case of the test rats and 46 days for the controls. An attempt was made to have the final weight in each pair of animals as nearly alike as possible. This was done by killing the heavier of the pair first (whether test rat or control), the other being allowed to live somewhat longer so as to approach its mate in body weight. The corresponding suprarenal glands might then be expected equal in the two rats, aside from changes due to compensatory hypertrophy. At the conclusion of the experiment the animals were killed with chloroform and the adrenals were removed and weighed separately.

The suprarenal glands after weighing were fixed in Helly's fluid (Zenker-formol), embedded in paraffin and cut in serial sections 5 micra in thickness. Courtney's dehydrating apparatus was found to be of advantage in securing good sections (2). Every tenth section was mounted. Mallory's triple connective tissue stain was used in each case. It gives good contrast between the cortex and medulla.

To determine the cortico-medullary ratios and percentages, Jackson's (3) modification of Hammar's paper weight volumetric method was used. In the present study the sections were projected at a magnification of 50 diameters.

In calculating the probable errors of the means, the usual (Pearsonian) formula was used, as given by Pearl (4).

BODY WEIGHT

The effect of the operation on body weight is shown in figure 1. The slightly greater drop in the adrenalectomized rats and their somewhat slower recovery is probably due to the effect of the operation rather than to any specific effect produced by the extirpation of one adrenal gland. It will be noted that the test rats continued below the controls in average body

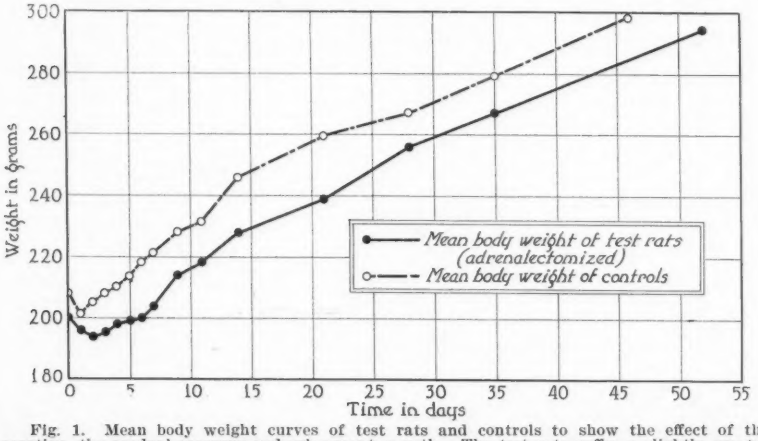

Fig. 1. Mean body weight curves of test rats and controls to show the effect of the operation, the gradual recovery and subsequent growth. The test rats suffer a slightly greater average initial loss, and thereafter increase steadily in weight but lag slightly behind the controls throughout the experiment.

weight, but reached nearly the same final weight because they were permitted to live a few days longer. The average final weight of the test rats was 293 grams (range 234 to 330), while that of the control rats was 298 grams (range 222 to 364).

MacKay and MacKay (5) found the weight curves of test and control rats after adrenalectomy to be nearly alike with apparently a slightly greater drop in the control group. Mann (6) observed no effect on body weight after unilateral adrenalectomy in rats.

SUPRARENAL WEIGHTS

Normal Growth. The right suprarenal glands of the adrenalectomized rat were weighed at operation. The mean weight was 0.0122 ±.0009 gram; range 0.0060 to 0.0170. The right suprarenal glands obtained at autopsy were also weighed. The mean for right gland in the normal controls at the end of the experiment was 0.0203 ± .0006 gram; range 0.0136 to 0.0262 gram, as shown in figure 2. The corresponding increase in the mean weight (0.0081 gram or about 66 per cent) represents the normal growth of the right suprarenal during the period of the experiment. The normal growth for the weight of one suprarenal gland according to the norm for the male Wistar albino rat during the corresponding increase in body weight is only about 0.0050 gram, as shown in figure 2, data from Donaldson (7). As appears in figure 2, the normal weights of the suprarenal glands in our

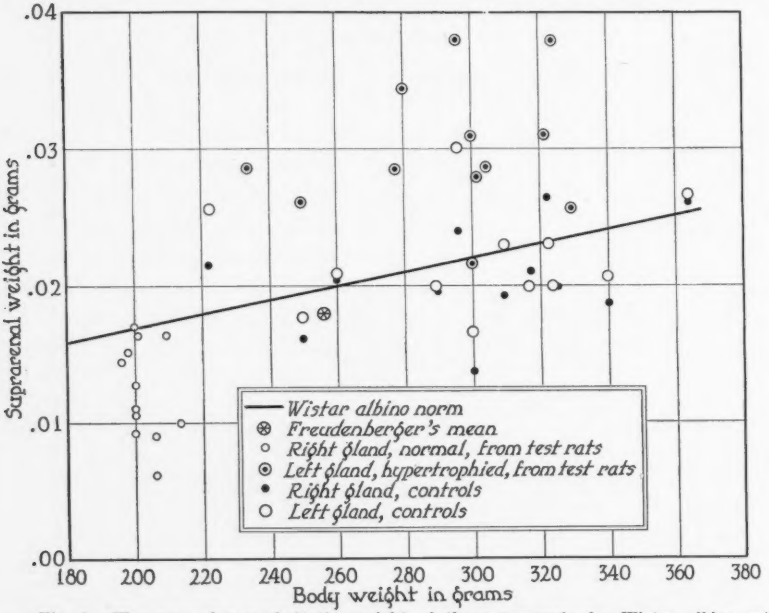

Fig. 2. The curve for one-half the weight of the suprarenals for Wistar albino rats (Donaldson) is shown. The weight of each suprarenal gland obtained in the experiment is also indicated. One-half of the average suprarenal weight of 33 other normal male Long-Evans rats from our colony is also shown (Freudenberger). The normal suprarenal glands in this experiment usually appear also below the Wistar norm, but the glands with compensatory hypertrophy are distinctly heavier.

Long-Evans rats average distinctly below the Wistar albino norm, as found also by Freudenberger (8).

Hypertrophy of the Left Suprarenal. In each case where the right suprarenal had been removed from a test rat, the remaining gland became heavier than the corresponding gland in the control. The average weight of the left suprarenal gland in the control animals at autopsy was .0219 ± .0002 gram; range 0.0164 to 0.0302, as shown in figure 2. The weight of the remaining left suprarenal in the test (adrenalectomized) rats averaged 0.0288 ± .0011 gram; range 0.0216 to 0.0378, as shown in figure 2. This represents an average increase of 0.0069 gram (or 31.6 per cent) in the weight of the left gland in the 12 test rats. The individual range of increase is from 0.8 to 55 per cent.

In the case of one of the adrenalectomized rats (No. 30-641) an accessory suprarenal was found closely related to the main suprarenal gland and apparently having the same blood supply. This accessory weighed 0.0133 gram. If this is included, the mean percentage of increase in weight averages 36 per cent (individual range 12 to 55 per cent) instead of 31.6 per cent. It is probably correct to include this accessory in the calculations because of its intimate connections with the main gland. (This has been done in the succeeding calculations and in the graph shown in figure 2.)

The occurrence of compensatory hypertrophy in the suprarenal gland is in general accord with the findings of most investigators in various species, as noted by Stilling (9), Simmonds (10), Wiesel (11), Strehl and Weiss (12), Carraro and Kuznitzky (13), Elliott and Tuckett (14), Kurijama (15), Mann (6), Specht (16), Kisch (17), Kojima (18), and Brauer (19). Kahn (20), Boycott and Kellaway (21) and Da Costa (22) obtained no suprarenal hypertrophy. Harley (23) was unable to find hypertrophy of the suprarenal gland in one rat that survived after many of his animals had died of infection.

Wiesel (11) in his study of 10 rats found apparent hypertrophy of the suprarenal gland in all except 2 of his animals. In 2 cases where he found no accessory suprarenals, the remaining gland was two to three times the size of the gland originally removed. The amount of hypertrophy in the other cases was not stated.

Mann (6) removed one adrenal in several species, including the rat. He usually found hypertrophy of the remaining gland.

MacKay and MacKay (5) extirpated alternately the left and right adrenal glands in 25 female albino rats at 90 days of age, using 25 controls with operation. They found the normal right gland in the control group to average 0.0238 gram and the left 0.0253 gram. In their test rats, after 40 days the hypertrophied gland averaged 0.0396 gram, representing an increase of 61 per cent. The greater apparent hypertrophy in their rats may be due to the difference in the strain of rats used, the sex, the diet or (possibly) the smaller number of animals in my series.

VOLUMETRIC DETERMINATIONS OF CORTEX AND MEDULLA

The average volume of the whole left gland in the test (adrenalectomized) animals, as represented by the mean paper weights, increased 32.4 per cent (30.7 per cent without the accessory of rat 30-641) in comparison with the controls. The volume of the cortex of the left gland averages 34.8 per cent (individual range 11 to 64 per cent) greater in the test animals than the average in the controls. The medulla similarly averages only 3.4 per cent greater in the adrenalectomized rats than in the controls. Of the compensatory suprarenal hypertrophy 99.2 per cent is therefore apparently due to an increase of the cortex. The compensatory hypertrophy of the cortex is therefore beyond doubt. But the relatively slight degree of hypertrophy in the medulla is of questionable significance. Tested statistically, the increase in the medulla was found to be only 1.4 times the probable error of the difference and is therefore insignificant.

If the values are expressed in percentages, it appears that the medulla of the left suprarenal in the test (adrenalectomized) rats averages 5.89 per cent of the total gland, while in the controls it forms 7.28 per cent of the total gland. If expressed in the terms of a ratio, the test (adrenalectomized) animals showed a cortico-medullary ratio of 16.0 to 1, and the controls 12.7 to 1. There is accordingly both an absolute and a relative increase in the cortex during compensatory hypertrophy.

That the compensatory hypertrophy of the suprarenal consists chiefly (or entirely) of cortex is in agreement with the results of Wiesel (11), the MacKays (5) and Mann (6) in the rat; and of Simmonds (10), Carraro and Kuznitzky (13), Elliott and Tuckett (14), Specht (16) and Kojima (18) in various other species.

Mann (6) has observed that hypertrophy of the medulla sometimes occurs. Borberg (24) has studied the medulla in other species, and does not believe that it shows any compensatory hypertrophy.

MacKay and MacKay (5) estimated the cortico-medullary changes from the areas measured in a single (central) section in 10 test and 10 control rats. In order to compare the results obtained by this method, the paper areas for cortex and medulla in the middle section of each gland in my series were taken and weighed separately. The average cortex of the test (adrenalectomized) animals by this method appeared only 21.9 per cent greater than that of the controls, while the medulla correspondingly appeared 11.8 per cent greater. The marked discrepancy is evident in comparison with the above-mentioned results obtained by the serial sections. The single section method therefore appears inaccurate, probably because the gland is somewhat irregular, with variations in the form and relations of the cortex and medulla at different places. MacKay and MacKay, using this single-section method found 91 per cent of the hypertrophy apparently due to the cortex. This is quite different from my finding of 99.2 per cent, using serial sections, which is obviously a more accurate though more laborious method.

Deansley (25), in studying the effects of toxins on the adrenals of mice, also compared the paper reconstruction method on single sections with results on serial sections. She found by using the short method a maximum error of 8 per cent in the whole gland. The cortex showed an error of 8 to 12 per cent. Nevertheless, she concluded that the short method is sufficiently accurate for most purposes.

SUMMARY

1. The right suprarenal gland was removed in 12 young adult male rats of the Long-Evans strain. Twelve control rats (litter mates) were subjected to the same operative procedure but without removing the suprarenal. After six to eight weeks the animals were killed. All the suprarenal glands were weighed separately. Cortico-medullary ratios were determined by Hammar's paper weight method from serial sections.

2. Following the operation there was a slightly greater loss of body weight in the test (adrenalectomized) animals. Thereafter the test rats increased steadily in weight but lagged slightly behind the controls throughout the experiment. All the rats remained healthy.

3. The left suprarenal gland at autopsy was found to average about 36 per cent heavier in the test (adrenalectomized) than in the control animals. This measures the extent of the compensatory hypertrophy during the experimental period.

4. The cortex in the left suprarenal gland of the test (adrenalectomized) rats averaged about 34.8 per cent greater than in the control animals. This accounts for 99.2 per cent of the hypertrophy in the whole gland. The smaller apparent increase of 3.4 per cent in the medulla is statistically insignificant.

5. The method of determining the changes in cortico-medullary relationships by the measurements from a single (middle) section is found to be unreliable.

This work has been done under the direction of Dr. C. M. Jackson, to whom I am indebted for many valuable suggestions.

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POSTURAL HYPOTENSION OCCURRING IN A NEGRO WITH ADDISON'S DISEASE

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In 1925 Bradbury and Eggleston (1) reported three cases of a condition which they termed "postural hypotension." Later Ghrist and Brown (2) described two patients apparently suffering from the same sort of disturbance, the outstanding features of which were syncopal attacks accompanying a marked fall in both systolic and diastolic blood pressure after changing from the supine to the upright position; slow pulse rate uninfluenced by change in blood pressure, anhidrosis, lowering of the basal metabolic rate, slight and indefinite changes in the nervous system, and increase of symptoms during the heat of summer. A similar case has been recently reported by Riecker and Upjohn (3).

This postural response of the blood pressure appears to be an exaggeration of the response which occurs in some normal individuals and which has been extensively studied by Crampton (4). It is possibly similar to the postural response of patients convalescent from long continued infectious diseases. None of the patients described in the literature had important concomitant disease, nor could their condition be explained on any known pathological basis.

The case here reported, an example of Addison's disease of the suprarenal glands, presented many of the features of postural hypotension.

CASE REPORT

On the 16th day of October, 1930, H. G., Negro, 50 years of age, came into Barnes Hospital complaining of vomiting, pain in the left flank, hiccoughing, and cough of 42 days' duration. His history was somewhat vague and was obtained with difficulty. He stated that his illness commenced when he was awakened in the middle of the night with generalized abdominal pain. Upon rising from his bed, he became dizzy and vomited. He attributed this to dietary indiscretion of the previous evening. He continued, however, to vomit three or four times a day and to suffer from abdominal distress. He lost strength and some weight, became extremely dizzy, and likely to lose his balance whenever he tried to stand.

A significant fact in the family history was that one brother had died of tuberculosis.

At the age of 19 the patient had gonorrhea, which recurred a few years later. When 28 years old he contracted malaria which lasted for 3 years. At 41 he had an attack of influenza which kept him in bed six or seven weeks, and from that time had a slightly productive cough each winter. He never had hemoptysis or pleurisy. Three years before admission, a gland said by his doctor to be tuberculous, was removed from his neck. Two years before admission he had entered Barnes Hospital for dilatation of a urethral stricture. He had been married 10 years, the marriage being childless.

Physical examination revealed a well developed and seemingly well nourished negro, 5 feet feet 10 inches tall, and weighing 172 pounds. He was lying comfortably in bed, so comfortably, in fact, and appearing so well that the

admitting officer considered him as a possible malingerer. Though the patient was not stuporous, he was quite wide awake, and answered questions slowly and vaguely, giving the impression of retardation of mental processes. The forehead was pigmented. His teeth were in bad condition. There were a few small areas of pigmentation on the soft palate and anterior pillars of the tonsils. A scar was seen on the left side of the neck just above the clavicle. Over the left apex the percussion note was dull, and breath sounds and spoken voice were diminished. X-ray examination of the chest showed increased hilus markings and calcified hilus glands. The cardiac impulse was neither seen nor felt. Percussion indicated a small heart. The sounds were distant. The rate ranged between 80 and 100. The rhythm was normal. With the patient supine, the blood pressure was 98/64. When he sat up on the side of the bed, he complained of not feeling well, and began to sway from side to side. His breathing became gradually slower and irregular and in three or four minutes he vomited. The systolic blood pressure taken during this episode dropped to 40-60, varying with respiration, and the diastolic became 0. When he was put back in bed the blood pressure returned to 98/64. The testicles seemed slightly atrophic. The deep reflexes were hyperactive and the Babinski extensor response and Oppenheim phenomenon were obtained on the left.

The composition of the urine was normal except for a few white cells. He had 4,000,000 red cells, 60 per cent hemoglobin, 7950 white cells, with 3 per cent eosinophils, 3 per cent stab. cells, 56 per cent segmented cells, 28 per cent lymphocytes and 10 per cent mononuclear cells. The non-protein nitrogen was 67 mgm. per cent, uric acid 4.7 mgm. per cent, blood chlorides 536 mgm. per cent, blood sugar 102 mgm. per cent, blood calcium 13.8 mgm. per cent, and phosphates 2.8 mgm. per cent. The serum albumen was 4.6 mgm. per cent and serum globulin 1.66 mgm. per cent.

It was found that the patient was comfortable and did not vomit when he was kept in the recumbent position. Thinking his a possible case of postural hypotension, we started to apply the tests employed by Bradbury and Eggleston, but were unable to complete them because of his increasing illness.

Using a postural drainage table, we obtained the following blood pressure readings and pulse rates:

Position	*Blood Pressure*	*Pulse*
Patient in horizontal position.....	98/64	100
Head down 80 degrees from horizontal...	86/64	92
Patient in horizontal position.....	92/64	90
Feet down 60 degrees from horizontal....	Not obtainable	Not obtainable

With the upright position, neither the systolic nor the diastolic pressure could be obtained and the pulse was imperceptible at the wrist. The patient vomited after four minutes.

His response to epinephrin was studied. He was given fresh epinephrin, 1-1000 solution, at the approximate rate of 0.1 mgm. per 1½ minutes until 0.7 mgm. had been administered. With small amounts there was no acceleration of the pulse rate nor any rise in blood pressure. After injection of 0.7 mgm. the pulse rate increased 20 beats per minute, the blood pressure rose 14 mm. systolic and 2 mm. diastolic, and the patient began to tremble as in a chill.

About one week after admission the patient's condition became notably worse. His temperature rose steadily; it had been normal except for a slight rise on his first day in the hospital. He became stuporous and refused nourishment. In spite of glucose and saline infusions and other therapy for shock, he died on the eleventh day of observation.

Autopsy revealed the following pathological conditions: There were numerous old adhesions in the upper half of the abdominal cavity binding the liver, spleen, stomach, diaphragm and kidneys. The peritoneal surfaces were elsewhere smooth and not injected. There was no free fluid. There were numerous old adhesions in both pleural cavities, more extensive on the right side. Numerous calcified miliary tubercles were seen throughout both lungs. The spleen was enlarged and firm, weighing 400 gms. and was firmly bound down by adhesions to the liver, stomach and pancreas. The liver and kidneys were considered normal on gross examination. A few of the mesenteric nodes were palpable, but not markedly enlarged.

The adrenals were embedded in a mass of adhesions and fat. The right adrenal was so firmly adherent that the liver had to be cut to free it. Both glands were almost stony hard, much enlarged and greatly distorted. The right gland weighed 17 gms., the left 27 gms. On section no normal cortex was seen.

Most of the gland was composed of hard fibrous tissue dull yellow in color, interspersed by the reddened vascular areas and the more deeply yellow areas of necrosis.

Microscopic examination of the thyroid showed extensive areas of scarring with infiltration with lymphocytes. No giant cells were noted. The acini were irregular in size, shape and colloid content. In the lung there were typical areas of tuberculosis with central necrosis, giant cells, epithelial cells and lymphocytes. The liver was spotted with small areas of necrosis with a peripheral reaction of giant cells, fibrin and round cells. There were many such tubercles varying greatly in size. The sinuses showed an occasional lymphocyte or large mononuclear cell. The capillaries of the kidneys were congested. There were several fibrotic glomeruli and several old scars with a great amount of lymphocytic infiltration which started in the cortex and ran in narrow zones radially towards the pyramids. The peripelvic connective tissue appeared edematous. The sentinal lymph nodes of the gall-bladder, a mesenteric and a peribronchial lymph node showed tuberculous foci.

Almost the entire adrenal gland was involved in a central mass of acute necrosis. Only one small nest of adrenal cells near the periphery remained. Surrounding this mass of necrotic material was a reaction zone containing giant cells, large mononuclears and lymphocytes intermingled with strands of fibrin. No acid-fast bacilli were demonstrated in Ziehl-Nielsen stain.

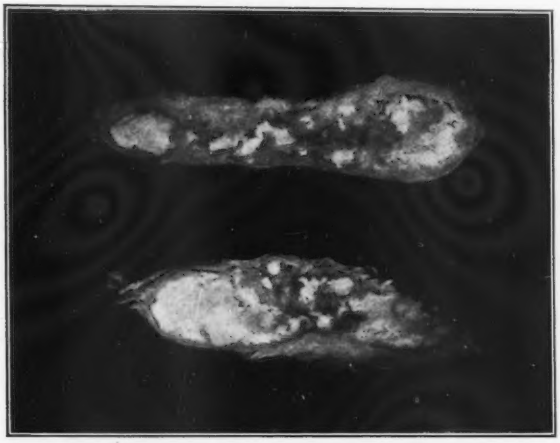

Figure 1. Sections of adrenal glands showing extensive tuberculous infiltration and destruction of glandular tissue.

Clinically this case presented the characteristic features of Addison's disease, asthenia, low blood pressure, pigmentation and gastric upsets. The pigmentation of the skin was doubtful and confusing and did not exceed or differ from that of patients in nearby beds in whom there was no suspicion of suprarenal disease. In the mucous membrane a few small patches of pigmentation were seen. Evans (5) has noted such areas in normally healthy negroes. A rather careful survey of the literature for the past forty-two years by Sala and Jacobi (6) has revealed only 4 instances in which Addison's disease was proven in the negro race. They reported the fifth case. This is in striking contrast to the high incidence of tuberculosis among negroes. Both Evans and Sala and Jacobi are agreed that the condition is probably more common than is indicated by records in the literature, the difficulty of recognizing pigmentation in the negro probably ex-

plaining in part the comparatively low incidence of recorded cases in the colored race.

Postural hypotension has been little emphasized in the description of Addison's disease although the phenomena which accompany it were apparently recognized by Addison (7) himself. In the description of his third case he says: "For the last month he has discontinued work on account of attacks of giddiness and dimness of sight, accompanied by a peculiar pain in the back of the head and partial loss of consciousness. These attacks would occur several times in the course of the day, upon any unusual exertion, always while in the standing posture, and were instantly relieved by sitting or lying down. Since he has discontinued his employment they have only occurred on getting out of bed in the morning." Later on, just a few days before the death of the patient, he says: "With these medicines and the middle diet he continued with no appreciable change until the 24th, when he had a kind of fainting fit upon rising to have his bed made, contrary to an order that he should keep in the recumbent posture."

Recently Ghrist (8) (9) has studied the effect of posture on several patients and one severe case showed minor changes varying from 78/58 to 60/54. In no instance was there an effect comparable to that which we have described.

It is unfortunate that in this patient studies were necessarily incomplete because of his poor general condition. An exact comparison of the findings to those of postural hypotension without Addison's disease cannot be fully made. Certain differences appear. Our patient's blood pressure dropped when he was in the "head down" position. There was some change in pulse rate with change in blood pressure. Vomiting did not occur when the patient assumed an upright position in any of the cases of Bradbury or of Ghrist. Many of the cases of postural hypotension show a sensitivity to adrenalin which was not apparent in our patient.

SUMMARY

Extreme postural hypotension may occur in Addison's disease and may increase the asthenia and aggravate the gastric symptoms. Study of the case which has been reported indicates that changes in position are accompanied by a tachycardia in which respect the condition seems to differ from that of idiopathic postural hypotension. In this case, also, there was no evidence of the anhidrosis which has distinguished cases of the idiopathic form.

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ADDENDUM

Since this report was submitted for publication, interesting comment upon the subject has appeared in the monograph by Rowntree and Snell (a clinical study of Addison's Disease). It is stated that in Ghrist's study of the postural phase of hypotension in Addison's disease both the "systolic and diastolic pressures fell to an indiscernable minimum" in two patients raised from the recumbent to the upright position. The pulse rate in all six cases became abnormally rapid during this change and, in one case, it became so rapid that it could not be counted.

DIFFERENTIATION OF THYROTOXICOSIS AND THE MENOPAUSAL DISTURBANCES

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Physiological disturbances at the time of the menopause may simulate any one of a number of recognized disease processes. The differentiation of true thyrotoxicosis from menopausal disturbances has been one of the puzzles which has not been subjected to attack in an objective way. The use of a single determination of the basal metabolic rate even when combined with a complete physical examination is not adequate to determine this separation in some cases. The problem can best be stated by citing an illustrative case.

Mrs. E. H., aged 48, was referred because her physician believed her to be thyrotoxic. She complained of precordial pain, with dyspnea and nervousness, which began one year previous to examination. Fatigue and weakness were increasing. Edema had been noted for 5 years, palpitation for one year. A goiter had been present for 20 years, with pressure sensations for 10 years. Increased sweating was reported. During the preceeding 11 months there had been one menstrual flow. The hot flashes were followed by vertigo and actual fainting.

Physical examination showed her to be well nourished, rather anxious, and visibly perspiring when nervous. The thyroid was nodular. Apical rales were heard on both sides. The pulse was always rapid. The blood pressure was 120 systolic, 70 diastolic. Tremor of hands, feet, and tongue was observed. Vague abdominal tenderness was recorded. The basal metabolic rate was 18 per cent above the predicted level (Aub-DuBois).

This patient was likewise thought to be thyrotoxic by the first member of the hospital staff who examined her. However, she was treated with bromide, amniotin (follicular hormone), and was not kept in bed. In one week the basal metabolic rate was 8 per cent above the prediction, the symptoms were relieved, and the patient was discharged.

The diagnostic problem here is perhaps more difficult for the consultant than for the family physician who has knowledge of the patient over a period of years. But even so, the onset of the thyrotoxic syndrome is notoriously insidious with adenomatous cases after the age of 40. The history of onset and the comparison with previous stability of the vegetative nervous system may not be an adequate basis for the diagnosis. The problem resembles the difficult differentiation between thyrotoxicosis and neurocirculatory asthenia. In the latter dilemma attempts have been made to distinguish the two syndromes by the temperature of the extremities, the presence of weakness in leg muscles, the various phases of the exophthalmic picture, as well as by the basal metabolic rate. Experience demonstrates that there is no one feature of either history or physical examination which may be depended upon for the separation. The basal rate is perhaps the best single criterion, but even this may be confusing since anxiety or failure to secure complete relaxation may give a high basal rate

in an individual with no metabolic disease. The attitude toward this problem expressed by Moschcowitz (1) affords a rational solution of the difficulty. The separation of the patients with "sensitive and emotional personality" alone from those with superimposed "Graves' syndrome" must depend very largely on the basal metabolic rate determinations. This implies a most dependable technical determination of the basal rate, by an operator who is able to secure complete cooperation of the patient. Moreover, it should include the ability to secure fairly constant metabolic rates on tests made on successive days or at short intervals, when no therapy other than bed rest has been used. Highly variable rates cause a suspicion of instability other than that due to the thyrotoxicosis.

In the "Graves' Syndrome" problem as stated by Moschcowitz the problem is one of deciding whether the patient has only this "sensitive and emotional personality" or whether in one of such type a hyperthyroid syndrome has been developed. This personality is assumed to be a part of the fundamental and permanent equipment of the individual. In the menopause the patient is usually to be described by similar terms, but the sensitiveness, emotional instability, and the vasomotor disturbances are known to be temporary manifestations, which will subside after a period varying from months to a few years. An adenomatous thyroid may be present in a patient with menopausal symptoms, without the thyroid tumor being at all responsible for the disturbance. Or an adenomatous thyroid may become toxic at this period of life, in which case the thyrotoxicosis may simulate the menopause prematurely or it may exaggerate the climacteric phenomena. The differentiation to be kept before the clinician is similar to that for younger patients, that is, the thyroid symptoms must be distinguished from what is for the time being a part of the patient's personality. Again the basal metabolism test will be found very useful here, if employed with the discrimination suggested above. But careful and detailed history taking, with the menopause in mind, will often be sufficient to make the diagnostic separation.

The occurrence of symptoms which are usually associated with thyrotoxicosis is frequent in patients who show menopausal phenomena without thyroid disease. The tabulation below of the occurrence of these various findings shows how a routine type of inquiry may confuse the picture. The seven patients represented were all referred because at least one physician had thought the patient thyrotoxic, although the clinical course leaves no doubt that none of them had symptoms due to thyroid disease. The symptomatic terms are used in the ordinary clinical sense.

SYMPTOMS IN SEVEN CASES SUPPOSED TO BE THYROTOXIC

Seven cases showed:

Goiter, for years
Recent increase in nervousness
Increased sensitiveness to heat

Six cases showed:
- Dyspnea
- Palpitation
- Increased sweating

Five cases showed:
- Tremors
- Weight loss, 5 to 25 pounds
- Menses irregular or absent for preceeding few months

Four cases showed:
- Weakness
- Easy fatigue

This tabulation overlooks the qualitative difference between the subjective temperature sensitiveness of the thyroid patient and that of the menopause patient. The thyroid type complains of a rather constant need for more ventilation, less clothing and less bed covering than before. The woman in the climacteric almost always tells of "hot flashes." Curiously, these periods of tenseness and warmth, followed after a few minutes by sweating and relaxation with relief, are better known to most women than to many of the younger medical men. Inquiry into the nature of this complaint about heat has proved to be the best key to the diagnosis so far as history taking can help. The other evidences of vasomotor disturbance are also frequently present for brief periods only, although the cyclic nature is not so commonly ascertainable from conversation with many patients.

It is not safe to make a diagnosis of menopause from menstrual irregularity or absence of menses alone. Thyrotoxicosis is not infrequently a cause for this type of disturbance, with resumption of normal periods after thyroidectomy. If menstrual irregularity or amenorrhea occur after the age of 40, with no pelvic lesions to account for the change, the menopause is the probable cause. But the possibility of true thyroid disease should still be considered until the clinical picture or, if necessary, the metabolic rate has made the decision certain.

Physical examination of such patients undoubtedly will help still further to make this differential diagnosis. There is no one feature which may be used as a touchstone. The eye-signs are even less important than in the younger patients. The tremors, sweating, tachycardia, and increased pulse pressure are equivocal since they may be seen in either condition. Many patients are aware of tachycardia during an office visit although the pulse rate is within normal range when there is no excitement. Nevertheless the completeness of the picture may settle diagnosis in many cases. In those women who remain problem cases the sceptical attitude toward a diagnosis of thyrotoxicosis is the conservative clinical position. Two steps are recommended: basal metabolism studies, repeated if not strictly normal at first, and therapeutic trial of the follicular hormone for relief of the menopausal symptoms.

In the seven cases referred to above the initial basal metabolic rates were from 8 to 24 per cent above the predicted normals (by DuBois standard). In the five who were re-examined within one week because of high rates the second determination dropped to 14 per cent or less above the normal. Experience with the laboratory has assured us that such drops are not common in thyrotoxic cases and that rates as high as 15 to 24 per cent above normal on first tests are significant. When such prompt decreases occur the change is to be attributed to an exaggerated apprehensiveness or nervous tension in the earlier examination. This type of personal attitude is seen in both thyroid disease and other sorts of emotional instability, but it is not readily removed in thyroid patients without very careful therapy. It is this sort of prompt decrease in basal rates after only a few days' use of follicular hormone therapy which gives objective certainty to the differentiation of the conditions.

The therapeutic test is not a new suggestion, but it has almost new possibilities since the introduction of the physiologically standardized preparations of the Graafian follicle hormone. Results in treatment of menopause cases as well as of a few other types of disturbance have already been published from this hospital (2). The cases mentioned above have been given marked relief by the use of "amniotin." Recent experience with "theelin" indicates that it is as effective in doses of comparable strength. The trial of either of these materials for a few days does not involve any prejudice to the diagnosis, nor does it commit one to a subsequent course of action as does the use of iodine. If the latter is successful it is now considered important to proceed at once to thyroidectomy, whereas if it is unsuccessful the diagnosis is not always settled by the attempt. In contrast the use of follicular hormone may clear the diagnostic problem, and it does not in any way affect the operability or other phases of treatment if the pathologic process is essentially in the thyroid. The decision can be made within the course of a week, at relatively little expense and inconvenience to the patient, and often with the necessity of surgery removed. Another case will illustrate how much change may occur.

Mrs. A. G., aged 55, was referred for treatment of thyrotoxicosis. Her goiter had been present for 15 years, but had increased in size for the past 6 months. The symptoms included nervousness, tremor, sweating, loss of 25 pounds, anorexia, weakness, and a feeling of warmth. Dyspnea, palpitation on exertion, and edema had been noted for 10 years. There were some indefinite dyspeptic complaints. Menstrual flow had ceased at the age of 50, but she still had hot flashes, and also anesthesias and paresthesias of the hands.

Physical examination revealed obesity, emotional instability, nodular goiter, extra-systoles, a systolic pressure of 140, and a diastolic of 75, and tenderness over the colon. There was a fine tremor of the fingers. The feet were wet and cold. The basal rate was 8 per cent above average normal.

The use of amniotin by hypodermic injection once daily, and later by the use of vaginal suppositories each night, gave such complete relief that the patient declined thyroidectomy. This was urged, although she was thought to be nontoxic. The extent of relief may be gauged by the change in attitude toward the surgery for which she had come to the hospital.

Thyrotoxicosis is such a striking clinical condition, with a therapeutic approach so concrete and often immediately necessary, that secondary diag-

noses may easily be overlooked in such patients. Therefore coincidence of thyroid disease with the climacteric deserves attention for another reason. Surgeons are giving increasing attention to the fact that often thyroidectomy stops the thyrotoxicosis but does not leave the patient completely well. The reason for this in many cases is evident from the discussion given by Moschcowitz (1). The personality problem is not changed by surgery, which removes only the major fraction of a hyperactive thyroid. In parallel fashion the thyroidectomy after the age of 40 will not prevent nor relieve greatly the vasomotor or other vegetative phenomena of the menopause. A further case will illustrate the problem, and indicate how treatment may be made more complete.

Mrs. C. S., aged 47, complained of loss of weight, nervousness for 2 years, sensitiveness to heat, sweating, metrorrhagia for 4 months, followed by irregular menses, fatigue, anorexia, nausea, vomiting, diplopia, amblyopia, and occasional vertigo. Palpitation and transient edema were recent. The complaints were more marked following tonsillitis a year previous to admission. Iodine had been administered recently.

Physical examination showed restlessness, sweating, exophthalmos, reduced convergence and winking of the eyes, symmetrical goiter with bruit and thrill, positive Riesmann sign, tremor of the tongue and hands, tachycardia, systolic murmur over the entire precordium, a systolic pressure of 148 and diastolic of 72, reflexes exaggerated, and quadriceps muscles evidently weak. The diagnosis of thyrotoxicosis was not doubted. The basal rate varied from 35 to 49 per cent above that predicted, and was not reduced by further iodine medication, with bed rest and sedatives.

Following thyroidectomy the basal rate dropped to 16 per cent above the average. The patient still complained of the hot flashes, restlessness and insomnia. These symptoms were relieved by the use of amniotin given 10 units at each of the two doses per day.

The dosage of the follicular hormone which has been found advisable has varied within rather small limits. A few patients have had adequate relief from 10 units per day. The largest doses employed for any length of time have been 20 units given morning and evening. Commonly the use of 20 units once in 24 hours in enough to abolish the hot flashes, or to make them very infrequent or minor in nature. It is surprising that in almost every case tried the use of the gelatin suppositories containing the hormone has been equally successful. This is with the understanding that the dose by suppository needs to be 2 to 3 times as large as by hypodermic route. But the relative prices of the material for the two routes of administration make the choice one of convenience rather than of cost.

SUMMARY

If the differential diagnosis between thyrotoxicosis and the menopause cannot be made by the history, physical examination, and careful use of basal metabolic rate determinations, therapeutic trials of the follicular hormone are indicated. Thyroidectomy may well be followed by such hormone therapy in cases where the two conditions coexist.

A grateful acknowledgement is made to the laboratories of E. R. Squibb & Sons for furnishing a large part of the amniotin used in study of these cases.

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A SYNDROME RESEMBLING FAMILIAL PERIODIC PARALYSIS OCCURRING IN THE COURSE OF EXOPHTHALMIC GOITER

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In the last five years, at The Mayo Clinic, four patients have been seen who had exophthalmic goiter, and who were subject to attacks identical clinically with those seen in the syndrome known as familial periodic paraylsis. To our knowledge, similar cases have not been reported in the English language. Further investigation of cases of this sort may eventually disclose the fundamental pathologic physiology of familial periodic paralysis, and possibly will help to solve some of the problems associated with the unique muscular weakness seen in exophthalmic goiter. Consequently, we felt that it was desirable to report these four cases. To date, the diagnosis of familial periodic paralysis has been made at The Mayo Clinic in only three instances, exclusive of the four cases under consideration.

Taylor stated that familial periodic paralysis has certain constant and cardinal peculiarities. Thus, it is characterized in its typical manifestation by hereditary transmission, periodicity, confinement to the motor portion of the nervous system, electrical changes, and finally, by the practically perfect health of the patient in the free intervals.

During a typical attack, the patient presents total or partial flaccid motor paralysis of all four limbs, and at times of the muscles of the trunk and neck. The muscles innervated by cranial nerves are practically never involved. Paralysis begins in the proximal portion of the limbs, usually in the legs, gradually progressing distally. After the height of the paralysis has been reached, there is a latent period, varying in duration, in which the degree of paralysis remains unchanged. Following this latent period, the paralysis disappears in reverse order to that in which it came on.

The onset of paralysis frequently occurs in sleep, the patient awakening partially or totally paralyzed. However, an attack may occur at any time in the day. The duration of an attack is from a few hours to two or three days, averaging eight to twelve hours. Both the onset and the cessation of an attack are gradual.

During an attack, the involved muscles are without excitability to galvanic, faradic, or mechanical stimulation, and there is total or partial loss of tendon reflexes. Sensation and sphincteric control are preserved intact. Many authors state that during an attack, examination of the heart frequently will reveal tachycardia, transient dilatation of the left ventricle, and a transient systolic murmur in the mitral area.

Except for the fact that the disease is usually familial, very little is known about its etiology. No constant pathologic changes have been found in the few cases in which postmortem examinations have been made. Various theories as to the etiology have been advanced, but none of these is entirely satisfactory. The disease was first considered to be of hysterical origin. Some observers considered it to be due to spasm of the anterior spinal artery. Recently the vegetative nervous system has been under suspicion. The possibility that it is essentially an endocrine disturbance has been advocated, especially by Shinosaki.

REPORTS OF CASES

Case 1. A man, 33 years of age, registered at the clinic July 9, 1927. There was no family history of periodic paralysis. One sister had been operated on at the clinic for exophthalmic goiter.

August, 1926, the patient had noted the onset of generalized weakness and nervousness. In October, he had begun to experience recurring periods of weakness of the legs in which it was difficult to cross one leg over the other. In February, 1927, he had noted tremor and tachycardia. March 17, 1927, he had experienced his first attack of generalized muscular paralysis; since that time, ten similar attacks of transient paralysis had occurred. Usually, for a day or so preceding an attack, there had been generalized muscular soreness, as though he had undergone unusual exercise. The attacks frequently had begun in sleep, although occasionally they had occurred in the day. The paralysis had started in the proximal portion of the limbs, usually in the legs first, and had progressed distally. The muscles supplied by the cranial nerves had never been involved in the attacks. The duration of the attacks had varied for from four to thirty-eight hours. Paralysis had been gradual in onset and in regression. There had been residual weakness for a day or so following each attack. In May, 1927, a diagnosis of toxic goiter had been made elsewhere. The basal metabolic rate had been reported as +91. Compound solution of iodine, 30 drops daily, had been administered for 15 days, during which time the patient had not experienced further attacks of paralysis.

On the day of the patient's arrival in Rochester he experienced a typical attack of periodic paralysis. He was immediately hospitalized for study and treatment. Examination revealed complete, flaccid paralysis of the muscles of all four extremities, and of the trunk. There was no paralysis of any of the muscles supplied by the cranial nerves. He was able to talk, swallow, and breathe normally. All deep and superficial reflexes were abolished. The involved muscles failed to respond to mechanical stimulation. Sensation and sphincteric control were intact. On percussion, the left border of the heart was found to be about 2 cm. lateral to the nipple line. Auscultation revealed a distinct systolic murmur in the mitral area. The pulse rate was 180 beats each minute.

There was a gradual return of muscular power over a period of sixteen hours. In leaving, the paralysis disappeared from the distal part of the extremities first. On the morning following the attack the patient stated that he still felt slight muscular weakness, although he was able to step up on an ordinary chair without help. Examination of the heart at this time failed to disclose any enlargement or audible murmur. The pulse rate was 95. All tendon reflexes were present and active.

There was symmetric enlargement of the thyroid gland, and the characteristic signs of exophthalmic goiter. The basal metabolic rate was reported as +41. Compound solution of iodine, 30 drops daily, was administered for a period of ten days, during which time the patient experienced no further attacks of paralysis. Subtotal thyroidectomy was then performed. Microscopic examination of a portion of the removed tissue disclosed hypertrophic parenchymatous changes. Postoperative convalescence was uneventful.

Three years after operation, we had the privilege of reëxamining this patient. At that time there was evidence that he probably was suffering from mild recurrence of exophthalmic goiter. He stated that he had experienced a few mild, abortive attacks of paralysis, lasting an hour or two, usually confined to a portion of one extremity, although he had never experienced further attacks of generalized paralysis such as he had had previous to operation.

Case 2. A man, 35 years of age, registered at the clinic, June 1, 1927. There was no family history of periodic paralysis. Three years prior to registration, following an attack of influenza, symptoms of exophthalmic goiter had developed and had persisted for six months. During that time a loss of weight of 30 pounds (13.6 kgm.) had occurred. From that time until six months prior to registration, he had considered himself to be in excellent health.

At the time of examination at the clinic the patient had a symmetric enlargement of the thyroid gland associated with the characteristic symptoms and signs of exophthalmic goiter. He had lost 50 pounds (22.7 kgm.) in weight; the pulse rate was 95. There was marked weakness of the quadriceps muscles, and the patient was unable to step up on an ordinary chair. The basal metabolic rate on two occasions was, respectively, +66 and +56.

In addition to the symptoms of exophthalmic goiter the patient complained of recurring attacks of flaccid paralysis, which had appeared in the course of both episodes of exophthalmic goiter, and from which he had been free in the interval of good health. He stated that the attacks usually had begun in the night, although they had occurred also in the day. During an attack there had been partial flaccid paralysis of the muscles of all four extremities, and of the trunk. The tendon reflexes had been found to be abolished. The muscles supplied by the cranial nerves had not been affected. During an attack he had been able to chew and swallow normally. Sensation and sphincteric control had been intact. The pulse rate had been found to be increased during an attack. On several occasions he had fallen to the floor and had been unable to rise. The duration of the attacks had been from two to forty-eight hours, averaging seven or eight hours. Attacks had occurred on the average of every two weeks.

While the patient was in the hospital undergoing observation and preoperative medical preparation with compound solution of iodine, he experienced two typical attacks of paralysis, occurring respectively on the fourth and the eighth day of the preparatory period. Following administration of compound solution of iodine, 30 drops daily, for a period of 12 days, subtotal thyroidectomy was performed. The microscopic diagnosis of removed tissue was of hypertrophic parenchymatous change. Postoperative convalescence was uneventful.

Six months after operation the patient was found to be in excellent health. The basal metabolic rate was +11. He has not experienced further symptoms of exophthalmic goiter nor has he suffered from further attacks of paralysis.

Case 3. A man, 30 years of age, registered at the clinic, October 14, 1929. There was no family history of periodic paralysis. In March, 1929, following an acute cold, he had noted the onset of weakness, anorexia, and loss of 30 pounds (13.6 kgm.) in weight. During the summer, he practically had regained his health and had regained the weight which he had lost. Two weeks prior to his registration at the clinic he had noted lameness and weakness of the quadriceps muscles, especially following a period of rest. This had disappeared on walking about. Two days prior to registration he had noted the onset of gradual, progressive weakness of the muscles of the extremities, which had extended until all four limbs were practically completely paralyzed. He had been brought directly to the hospital, for it was feared that he might be suffering from an acute attack of poliomyelitis.

Examination revealed bilateral, symmetric weakness of the muscles of the limbs and trunk, especially marked about the pelvic girdle. The tendon reflexes were practically abolished. Examination of the spinal fluid gave entirely negative results, within a few hours the paralysis had entirely subsided, and the tendon reflexes were normal. At that time, the patient was able to step up on an ordinary chair without help. General physical examination revealed symmetric enlargement of the thyroid gland and the characteristic signs of exophthalmic goiter. The pulse rate ranged from 112 to 124. The basal metabolic rate on two occasions was +46 and +48. Compound solution of iodine, 30 drops daily, was given for twelve days, during which time there were no further attacks of paralysis.

Subtotal thyroidectomy was performed. The microscopic diagnosis of removed tissue was of hypertrophic parenchymatous change. Postoperative convalescence was uneventful. Ten days after operation the basal metabolic rate was —6. Since that time the patient has presented no further evidence of exophthalmic goiter, nor has he experienced further attacks of paralysis.

Case 4. A man, 29 years of age, registered at the clinic, January 6, 1930. There was no family history of periodic paralysis. One brother had been operated on elsewhere for exophthalmic goiter. The patient had been in excellent health until February, 1928. At that time he had noted weakness and tremu-

lousness of the legs. A month later, on awakening one morning, he had found that he was completely paralyzed in the muscles of all four extremities and of the trunk. There had been no involvement of the muscles supplied by the cranial nerves. He had been able to talk and to swallow normally. Sensation and sphincteric control had been preserved. The tendon reflexes had been found to be absent. By noon of that day the paralysis had disappeared and the reflexes had responded normally. At this time, he had noted that he was losing weight, although he had a ravenous appetite, that he was nervous, and that he had tachycardia. A diagnosis had then been made of exophthalmic goiter. The basal metabolic rate had been reported as +72. He had been given compound solution of iodine for seventeen days. This had been followed by a series of treatments with roentgen rays, applied over the thyroid gland. He stated that he had made immediate improvement, and by June, 1928, had regained his health. Following an attack of scarlet fever, in September, 1929, he had noted nervousness and beginning exophthalmos of the left eye. During the same time he had experienced occasional recurring attacks of paralysis, none of which had been as marked as that which he had experienced in March, 1928.

General physical examination revealed symmetric enlargement of the thyroid gland and the characteristic signs of exophthalmic goiter. The pulse rate was 92. Basal metabolic determinations on four occasions were reported as +25, +12, +16, and +14. There was no objective evidence of disease of the central nervous system. A diagnosis was made of exophthalmic goiter. Compound solution of iodine, 30 drops daily, was administered for a period of 14 days, at which time the basal metabolic rate on two occasions was reported as +8 and +3. Since the patient's symptoms of exophthalmic goiter were alleviated by the administration of compound solution of iodine, operative procedures were not conducted.

Since that time the patient has experienced no further symptoms, nor has he shown clinical signs of exophthalmic goiter. Likewise, he has not had further attacks of paralysis.

COMMENT

Seven patients have been seen at the Clinic who have presented symptoms and signs which are considered characteristic of the syndrome known as familial periodic paralysis. All of the patients were males. In no case was a family history of the disease obtained. Four of the seven patients were found to be suffering from exophthalmic goiter. In these cases the attacks of paralysis were identical to those experienced by the three patients who did not give evidence of disease of the thyroid gland. It is stated in the literature that the onset of the attacks usually occurs in the second decade of life. In the three cases in which there was no evidence of disease of the thyroid gland, the attacks had started at the ages of 11, 12 and 15 years, respectively. In none of the cases associated with exophthalmic goiter had attacks of paralysis occurred prior to development of the symptoms and signs of exophthalmic goiter. The onset of paralysis in this group had occurred later in life than in the cases in which there was no evidence of disease of the thyroid gland; the youngest patient in this group was 28 years of age at the time of onset of his first attack of paralysis. Three of these patients gave histories of two distinct episodes of hyperthyroidism, during both of which they had experienced recurring attacks of paralysis. In the period of remission from the hyperthyroidism, none of the patients had experienced attacks of paralysis. Two of these patients experienced complete relief from hyperthyroidism and attacks of paralysis following subtotal thyroidectomy. Another patient had experienced similar relief through control of the exophthalmic goiter by

means of roentgen therapy and the administration of compound solution of iodine. The fourth patient in this group, who was not entirely relieved of the recurring attacks of paralysis by resection of the thyroid gland, was believed to be suffering from mild recurrence of the exophthalmic goiter. Thus, it would appear that the recurring attacks of flaccid paralysis in these four cases of exophthalmic goiter were dependent on the existence of the latter disease.

It is known that patients suffering from exophthalmic goiter frequently display marked muscular weakness. This may be demonstrated in the loss of power of the quadriceps muscles, as illustrated by the difficulty with which a patient steps on a chair. The patient is frequently unable to accomplish this without assistance. In like manner, the patient frequently experiences considerable difficulty in arising from a sitting posture. We have had patients suffering from exophthalmic goiter at times complain of their legs transiently giving way and of their falling to the ground. They have usually been able to arise immediately and proceed on their way. We have noted also in occasional severe cases of exophthalmic goiter, marked weakness of the bulbar group of muscles, producing difficulty in deglutition and phonation. Occasionally, patients suffering from exophthalmic goiter have ocular palsy, and even at times ptosis, which may or may not be associated with exophthalmos.

Charcot first described the occurrence of paraparesis and paraplegia in the course of Basedow's disease. He stated that the great physical weakness of which the patient suffering from exophthalmic goiter complains is partly the result of emaciation, but that there also is actual motor weakness, sometimes chiefly in the legs, which may be so marked, or so much increased as to cause collapse of the patient. Möbius defined the condition as characterized by flaccid weakness or paralysis, by diminution or loss of tendon and skin reflexes, and by preservation of sensation and sphincteric control. He stated that the occurrence of paralysis depends on the severity of the Basedow's disease and that on regression of the Basedow's disease the paralysis disappears. Oppenheim stated that Saenger and Edenger had told him that they had noted the occurrence of periodic paralysis in association with exophthalmic goiter.

Shinosaki reported a study of 24 cases of periodic paralysis; 15 cases (62 per cent) were associated with goiter, in seven of which (29 per cent) the diagnosis was Basedow's disease and in eight of which (33 per cent) the diagnosis was of simple struma without Basedow's disease. In one of his cases, diagnosed as exophthalmic goiter and periodic paralysis, the patient died following an attack of grippe, and necropsy was performed. The thymus was reported as being persistent and enlarged. There was diffuse parenchymatous hypertrophy of the thyroid gland. Microscopic studies of the parathyroid bodies, the hypophysis, the suprarenal glands, the pancreas, skeletal muscles, and the spinal cord, failed to disclose any notable changes.

In six of seven cases of periodic paralysis in which Shinosaki administered thyroid extract in relatively large doses over a prolonged period of time, he noted a definite increase in the frequency and severity of the attacks of paralysis. As a control, thyroid extract was administered in similar doses and over a like period of time to three normal persons, but they did not have attacks of paralysis. By administration of epinephrine to one group of subjects and of parathyroid extract to another, Shinosaki was able to increase the frequency and the severity of the attacks of periodic paralysis. In the latter instance, positive results occurred in a smaller percentage of cases and in a milder degree than resulted from the administration of thyroid extract.

It occurs to us that there are two plausible explanations of recurring attacks of paralysis in association with exophthalmic goiter. It is possible that the patient may have a latent tendency to the development of true familial periodic paralysis, in which instance the exophthalmic goiter may act merely as an inciting factor to precipitation of the attacks. A more plausible theory is that there may be some physiologic or chemical change, at present not understood, which occurs in the muscle tissue in cases of exophthalmic goiter and which is directly responsible for the production of transient flaccid paralysis.

SUMMARY

In four of seven cases seen at The Mayo Clinic in which a diagnosis of periodic paralysis had been made, there was associated exophthalmic goiter. In these cases, the attacks of paralysis apparently occurred only in the active stage of exophthalmic goiter, and disappeared when the exophthalmic goiter had been controlled by medical or surgical measures. The four cases are described.

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DESTRUCTION OF THE DEPRESSOR ACTION OF ADRENALIN BY ULTRA-VIOLET RADIATION

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As a result of the work of Hoskins and McClure (1) Cannon and Lyman (2), Hartman (3), Moore and Purinton (4), it is now recognized that small amounts of adrenalin produce a fall in blood pressure, an effect directly opposite to that of large amounts as observed by Oliver and Schäfer (5) and Szymonowicz (6).

This investigation was begun to determine what effect if any ultra-violet radiation would have on the depressor action of adrenalin and the following is a description of the method of precedure in carrying out the experiments. A 1:750,000 solution of a commercial preparation of adrenalin chloride (Parke, Davis & Co.) was exposed at a distance of 15 cm. to the radiation from a Cooper-Hewitt quartz-mercury burner operating at approximately 140 volts, 3.3 amperes, for various lengths of time. The vessel containing the adrenalin was immersed in running water during the irradiation to prevent heating and evaporation. Dogs anesthetized with ether were used in this work. Two tenths of a cubic centimeter of adrenalin per kilo of body weight was injected. The injections were made into the external jugular while blood pressure records were being taken by means of a mercury manometer from the carotid artery. Approximately ten seconds was required for an injection.

The following is a description of a typical experiment. Twenty cubic centimeters of adrenalin chloride diluted 1:750,000 was introduced into a flat bottomed glass dish about five centimeters in diameter. This was placed under the quartz burner at a distance of 15 centimeters in running water to keep the solution cool and to prevent evaporation during the exposure. Three cubic centimeters of the solution was removed before the irradiation began, which served as a control. The burner was then started and after five minutes three cubic centimeters more of the solution was removed. Similarly after 7, 10, 12, and 15 minutes of irradiation, other three cubic centimeter portions were removed. Two-tenths of a cubic centimeter per kilo of body weight of these solutions irradiated for the different periods of time, as well as the non-irradiated solution, was introduced into the external jugular of the dog and blood pressure records were made as described above. The results of these determinations are shown in Fig. 1. It may be seen that the control or non-irradiated adrenalin produced a marked depressor action; that the solution irradiated for five minutes produced a smaller depressor effect; that the solution irradiated for seven

minutes a still smaller depressor effect; while that irradiated for fifteen minutes had no depressor action. Several experiments similar to the preceding were carried out with comparable results.

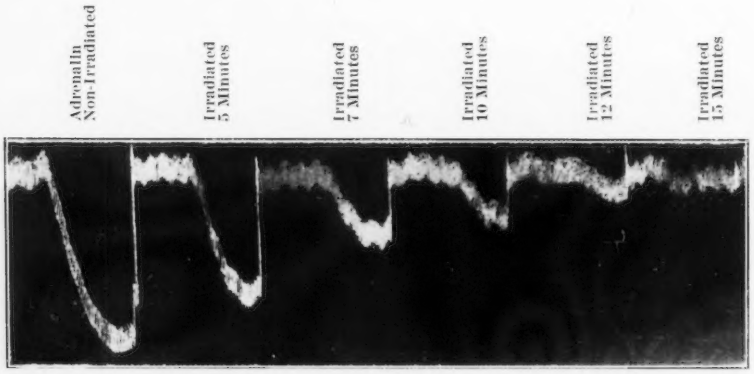

Fig. 1. Chart showing that Ultra-Violet Radiation destroys the depressor action of adrenalin.

SUMMARY

1. A 1:750,000 solution of adrenalin chloride was irradiated at a distance of 15 cm. for 5, 7, 10, 12 and 15 minutes, respectively.

2. Two-tenths of a cubic centimeter per kilo of body weight of these solutions, and of the non-irradiated solution, was introduced into the external jugular of a dog and blood pressure records were made.

3. The non-irradiated adrenalin produced a marked depressor action; the depressor effect was lessened with each increase of irradiation and had disappeared after 15 minutes.

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Abstract Department

The depletion of muscle sugar by adrenalin. II. Bischoff, F. and M. Louisa Long, Am. J. Physiol. **90:** 403. 1930.

By means of the continuous intravenous injection method, the time of adrenalin activity was accurately established. The experimental technique was otherwise the same as described in a previous paper. Muscle glycogen and hydrolyzable sugar and blood lactic acid were also determined. A fall in muscle sugar below the resting level is observed during the recovery period following a subcutaneous or continuous intravenous dose of adrenalin. The effective subcutaneous and continuous intravenous muscle sugar lowering doses of adrenalin are the same. The minimum muscle sugar lowering dose of adrenalin is greater than the minimum hyperglycemic dose. A physiological rate of injection over a long period of time reduces the muscle sugar below normal. When the muscle sugar was observed to be low following the action of adrenalin, the muscle glycogen was also low, but normal or high muscle sugar values were found with low muscle glycogen values. Under conditions in which blood sugar, muscle sugar, and muscle glycogen were affected by adrenalin, the polysaccharide sugar of the muscle was unaffected. It is suggested that during adrenalin activity a reserve of unknown chemical constitution is depleted in the muscles and that during the recovery period the muscle sugar is rapidly utilized either to build up this store or take its place.—Authors' Abst.

The influence of the adrenals on the blood picture (Einfluss der Nebennierenrinde auf des Blutbild). Catel, W. and M. Jedas, Monatschr. f. Kinderh. **47:** 301. 1930.

The authors have made a clinical study of the effect of raw adrenal cortex brei on the hemoglobin and the erythrocyte count in prematurely born infants and young children with secondary anemia. The study included 22 cases in all. The daily oral administration of 6 grams of adrenal cortex brei for 14 days produced a rise in the red cell count of approximately 1 million and an accompanying increase in hemoglobin of about 1 gram. In the premature born infants the results were less conclusive but generally tended in the same direction. Larger doses produced somewhat correspondingly larger increases.

—K. A. Brownell.

On the adrenals in hypertension and arteriosclerosis (Über die Nebennieren bei Hochdruck und Arteriosklerose). Goldzieher, M., Virchows Arch. f path. Anat. **280:** 749. 1931.

The paper reviews previously published facts about the rôle and changes of the adrenals in cases of hypertension and arteriosclerosis. The greater adrenalin content of such glands and the constant hypertrophy of the musculature of the adrenal veins are considered as the most important findings. Nodular hyperplasia of the cortex is frequently found but the opinion prevails that this has no relation to the development of hypertension. Changes in size, particularly enlargement of the adrenals, were found by numerous authors, but their occurrence is not constant and therefore not regarded as significant. The same applies to diffuse hyperplasia of the adrenal medulla. Fifteen cases of hypertension are described in this paper in 7 of which an enlargement and in 2 a decrease in size was noticed. The hyperplasia of the medulla was present in all these cases even though the glands appeared to be smaller than normal. Atrophy of the cortex is held to be responsible for the decreased volume of these glands. Such atrophy as a rule occurs in the more advanced cases of arteriosclerosis. The medullary tissue consisted of strands and sometimes syncytial groups of chromaffin cells. The individual cells are conspicuous for their polymorphous appearance and great variety of size. Unusually large and even gigantic nuclei are also met with. Two cases of this series showed multiple nodules in the medulla consisting of chromaffin cells. These nodules are analogous in structure to some of the larger tumors of the adrenals which are known to be accompanied by hypertension. The paper does not claim that adrenal hyperfunction and excessive discharge of adrenalin is the cause of hypertension and arteriosclerosis, but emphasizes that pathological hyperfunc-

tion of the adrenal glands should be considered among the factors which are capable of eliciting hypertension and subsequent impairment of the arteries. —Author's Abst.

Protection of adrenalectomized animals against bacterial intoxication. Hartman, F. A. and W. J. M. Scott, Proc. Soc. Exper. Biol. & Med. **28**: 478. 1931.

Cortin, the extract of the adrenal cortex, significantly increased the resistance of bilaterally adrenalectomized rats to bacterial intoxication, caused by injection of 1.5 cc. of typhoid vaccine (1.5 billion killed organisms).—M. O. L.

Increased resistance to cold produced by cortin after adrenalectomy. Hartman, F. A., Proc. Soc. Exper. Biol. & Med. **28**: 702. 1931.

Adrenalectomized rats treated with cortin were able to maintain body temperature better than similar ones treated with the same volume of isotonic saline solution, and nearly as well as normal controls. Hartman suggests that the adrenal cortex has some function in the maintenance of body temperature. —M. O. L.

The cells of the suprarenal cortex in the guinea-pig. Their reaction to injury and their replacement. Hoerr, N., Am. J. Anat. **48**: 139. 1931.

The normal suprarenal as well as glands modified by chloroform narcosis, diphtheria toxin, mustard gas, scorbutic diet, cauterization, vessel ligation or partial ablation, were studied. It was found that the cells of the suprarenal cortex have a short life history. They are continually dying in the zona reticularis, and being replaced by cells produced by cell division in the outer levels of the cortex mainly at the border of the glomerulosa and fasiculate zones. The early stages of cells normally degenerating through senescence in the zona reticularis are the so-called light and dark cells. The rate of cell destruction and proliferation can be greatly accelerated by the injection of toxins, bacterial suspensions, metallic poisons, etc. If the lesions are not so severe as to cause a great injury to the supportive tissue, and thereby a reaction from the fibrogenic elements (scar formation), they are rapidly repaired by a removal of necrotic débris and replacement with sound cells from the outer zones of the cortex. Repair is usually effected within a week from mild injuries, and nearly always within a month from more severe damage.—W. J. A.

Transplants of adrenal cortex into rat ovaries. Pencharz, R. I. and J. M. D. Olmstead, Proc. Soc. Exper, Biol. & Med. **28**: 600. 1931.

Adrenal cortex transplanted into the ovaries of 6 adult rats successfully maintained life after bilateral adrenalectomy. The operations were carried out in two stages, (1) removal of one adrenal and transplantation of a portion of it into an ovary, and (2) removal of the second adrenal some time following the first operation.—M. O. L.

The lactic acid metabolism in pregnancy and its relation to carbohydrate metabolism, to the function of the liver and thyroid gland and to the circulation. I. What is the source of the lactic acid increase in the blood of pregnant women? (Über den Michsäureumsatz in der Schwangerschaft und seine Beziehungen zum Kohlehydratstoffwechsel, zur Leber-und Schilddrüsenfunktion und zum Kreislauf; woher stammt die Milchsäureerhöhung im Blut von Schwangeren?) Anselmino, K. J. and F. Hoffmann, Arch. f. Gynäk. **142**: 289. 1930.

II. The cause of the increased formation of lactic acid in the muscles of pregnant women (Über die Ursachen der vermehrten Milchsäurebildung im Schwangeren-Muskel). Ibid. 310. Abst., Chem. Absts. **25**: 731.

The increase of lactic acid noted in the blood of pregnant women towards the end of pregnancy might be due to a failure of the liver to remove the lactic acid from the blood or to an increased formation of lactic acid in the placenta or the muscles. Injections of lactic acid showed that the liver of pregnant women is quite as able to dispose of lactic acid as the liver of non-pregnant women. It has been shown that the placenta is not the source of any considerable amount of lactic acid. Pregnant women doing light work were found to have more lactic acid in the blood than non-pregnant women doing similar work. It is probable, therefore, that the muscles are the source

of the increase of lactic acid towards the end of pregnancy. Soon after delivery the lactic acid formation from the muscles returns to normal. The increased production of lactic acid in the muscles of pregnant woman as compared to the non-pregnant woman might be due to a deficient supply of oxygen or to a change in the regulation of carbohydrate metabolism. No relation was found between the oxygen content and the lactic acid content, while the percentage use of oxygen directly after work was greater in the pregnant than in the non-pregnant woman. Physiological and clinical studies indicate that in pregnancy there is a hormonal change in regulation of carbohydrate metabolism which through an increased function of the thyroid gland leads to an increased production of lactic acid in the muscles both when at rest or at work.

Hemophilia and the female sex hormone. Birch, C. L., J. A. M. A. **97**: 244. 1931. Abst., A. M. A.

The author tested the urine of five hemophilic persons for the female sex hormone. From his observations he concludes that the urine of patients with severe hemophilia is deficient in the female sex hormone.

The anterior-pituitary-like hormone of the human placenta. Collip, J. B., D. L. Thomson, M. K. McPhail and J. E. Williamson, Canad. M. A. J. **24**: 201. 1931.

Extracts of this principle of the human placenta have been prepared by a method embodying the principle of the technique employed by Zondek and Aschheim and by Biedl for extracting the principle from pregnancy urine. The effects following injection of such extract into male and female rats have been compared with those following daily intramuscular implants of rat pituitary into such animals. The extracts produce a consistent acceleration of growth of the accessory sex organs in immature rats of both sexes, but do not affect castrates, whence it may be concluded that the intact gonad plays an essential part in the reaction. The results on the male are in marked contrast to the comparative inactivity of emmenin. The ovaries of young animals do not as a rule increase in size to such an extent that they become larger than those of normal adults, nor do normal adult females which have received intensive treatment with these extracts usually show hypertrophy of the ovaries. The implant treatment produces a remarkable effect on the weight and histological appearance of the ovaries of immature females, much greater than that due to placental extracts. A less striking difference is exhibited by the effect on the male gonad. The difference in results may be interpreted as either a matter of dosage or due to the absence of some specific growth promoting effect in the placental material.—A. T. C.

Recent observations on the ocytocic properties of blood from women in labor (Nouvelles recherches sur les propriétés ocytociques du sang de la Femme en travail d'accouchement). Fontes, J., Compt. rend. Soc. de biol. **103**: 349. 1930.

Blood taken from women in labor contains an ocytocic substance, which is not present if the blood is taken a few hours later. This substance is present in the blood of the mother but not in that of the fetus. Possibly the placenta is its source. The guinea pig uterus was used as an indicator.—J. C. D.

Irradiation of the ovaries of guinea-pigs and its effect on the oestrous cycle. Genther, Ida T., Am. J. Anat. **48**: 99. 1931.

Young virgin guinea-pigs, in which one or more normal cycles had been observed, were used. The usual weight at the time of irradiation was between 350 and 500 grams. Sterilization required much higher dosage than is considered effective for women. Excluding animals which died within a week or ten days following exposure to a very strong dosage, there can be distinguished two important types of alteration in the function of the sexual organs: (1) degeneration of large and small follicles together with the contained egg cells, and subsequent hypertrophy of the theca interna, so that the greater portion of the ovary became permeated with interstitial material. Very few primordial follicles remained in such ovaries. However, some follicles continued to mature, partially or completely, but in a very irregular manner. Oestrus cycles continued in these animals, but were very irregular in length. Whenever

oestrus occurred at least one large follicle was found in the ovary. (2) Atresia of all follicles, except some of the primordial ones; later a fibrosis of the ovary occurred with shrinkage of the organ as a whole. In these ovaries the uninjured primordial follicles developed subsequently into small follicles, but these degenerated as soon as formed, so that medium or large follicles were never found. In this group sexual cycles were absent and the genital tract was in a continuous resting condition, becoming atrophied in about one month after irradiation. In all cases the follicular elements were first affected by the x-rays. On the whole the corpora lutea were very resistant to irradiation. The germinal epithelium and the tunica albuginea remained unchanged. These experiments support the generally accepted view as to the importance of the follicular hormone in initiating oestrus. The necessary hormone is elaborated by the maturing follicles, regardless of the character of the rest of the ovarian tissue. Furthermore, confirmation is given to the conception of the function of corpus luteum as a regulator of the sexual cycle. This structure prevents ovulation and tends to counteract the effects of the follicular hormone; in its absence the cycle depends on the growth and function of the follicles only.
—W. J. A.

The relation between the anterior pituitary body and the gonads. Part 1. The factors concerned in the formation of the corpus luteum. Hill, M. and A. S. Parkes, Proc. Roy. Soc., London (B.), **107**: 30. 1930.

Rabbits were kept alone for 2-3 weeks and a laparotomy performed to determine whether ripe follicles were present. The animals were then injected with an extract from the urine of pregnant women and laparotomy performed in 15-18 days to ascertain whether ovulation had taken place. Ovulation occurred and functional corpora lutea were formed. The pseudo-pregnancy produced was of normal length. These experiments show that the stimulus required for luteinization of the ruptured follicle is initiated by ovulation and not as an effect of copulation.—E. L.

The relation between the anterior pituitary body and the gonads. Part III. Fractionation and dilution of ovary-stimulating extracts. Hill, M. and A. S. Parkes, Proc. Roy. Soc., London (B.), **107**: 455. 1931.

The tests were made on immature mice. The extracts were prepared from pregnancy urine by alcoholic fractionation. The material soluble in 50% alcohol was predominantly luteinizing and the material soluble in 30% alcohol mainly caused follicular maturation. These two reactions were proved to be due to different hormones and not due to one hormone producing different responses due to different concentrations.—E. L.

Experimental investigation of the function of the hypophysis in the dog (Experimentelle Untersuchung der Hypophysenfunktion beim Hunde). Koster, S. and A. Geesink, Arch. f. d. ges. Physiol. **222**: 293. 1929.

From the results produced in 9 adult and 14 young dogs in which the pituitary glands were removed, the authors conclude that the ablation caused cessation of growth, retention of the puppy form of hair, derangement of the calcium metabolism, lowered blood sugar, lowered oxygen consumption, lowering of about 1 degree Centigrade of body temperature, normal morphology of the blood and checking of the primary and secondary sexual characteristics. Microscopically, there was a decided hypertrophy of the pars tuberalis and the accessory hypophysis.—E. L.

Vitamin E and the production of testicular hormone (Das vitamin E und die produktion des testikularhormons). Kudrjaschov, B. A., Endokrinologie, **7**: 91. 1930.

Male rats at different ages were kept on diets deficient in vitamin E for periods up to 300 days; 95 animals were employed. The testes of such male rats exhibited gradual degenerative changes, arranged by the author in 5 stages, which resulted finally in a loss of the spermatogenetic tissues of the organs; there was a parallel decrease in testis weight, and in size of the seminal vesicles and prostate gland. The interstitial tissue of the testis was unchanged. Since diminution in size of the accessory organs was similar to that in castrated animals, and since only the spermatogenetic elements of the testes were changed, the author believes the evidence is good that hormone production is associated with the spermatogenetic tissues and not with the interstitial tissues.—C. R. Moore.

The regulation of production and the function of the male sex hormone. Moore, C., J. A. M. A. **97**: 519. 1931. Abst., A. M. A.

There is no single criterion or set of criteria that clearly indicates in man a hypogonodal state of the testicle. When objective means have been found that bridge this difficulty, the way will be opened for sane procedure. It cannot be too strongly emphasized that in this field of investigation subjective indexes are misleading and independable. As to the effect of the hormone on the testicle, it may be said in general that no endocrine gland has been proved to be stimulated by an internal secretion which the organ itself produces. Specifically in regard to the testis, he has dealt in his laboratory with many mammals whose testes have been experimentally injured both for germ cell and for hormone production. He has never been able to detect any stimulating effect on these or on normal testes from the injection of potent doses of male hormone. On the contrary, the normal testicles of young rats have been injured and held back in their development when the male hormone was administered. He has found that daily injections of male hormone into rats at the age of puberty, for a period of two weeks, causes a loss in weight of the testicles of 50%, and histologic study reveals pronounced injury. Such an injury is regarded as indirect by virtue of a reciprocal action between the hypophysis and the gonads. Excessive administration of sex hormone, male or female, appears to depress the sex stimulating secretion of the hypophysis, and in the absence of, or diminution of, the hypophyseal secretion the sex glands are injured. This is equally true for the female since administration of female hormone instead of stimulating ovarian activity actually injures the ovaries materially. Male hormone, thus administered to males, does not repair testis damage, though it does have a marked action on the accessory organs of reproduction. The testicle can be stimulated to excessive hormone production by administration of fresh hypophyseal implants or active hypophysis secretion, but there is no evidence that the male hormone in any way stimulates the testicle.

The effect of morphine poisoning upon growth, the oestrus cycle and fertility of the white rat. Myers, H. B., J. Pharmacol. & Exper. Therap. **41**: 317. 1931.

Morphine suppresses the menstrual cycle and sexual desire in a habituated woman and is sometimes reputed to cause sterility during the habituation. It has been stated that rats fed morphine grow more rapidly than control animals for a few weeks, then rapidly lose weight and die. Female white rats were made tolerant to morphine to determine what effect it might have upon the oestrus cycle, fertility and growth. It was found that morphine tolerant rats continue to exhibit the oestrus cycle with but slight irregularity. They mated, conceived and bore young of healthy appearance in numbers equal to the litters of control rats. The morphine tolerant rats were found to have a uniform growth curve approximately 90% that of control litter mates. Mature rats likewise were found to have a weight curve, while tolerant to morphine, approximating 90% that of control female litter mates over a period of twenty weeks, at which time the experiment was concluded.—H. B. Myers.

The functions of the corpus luteum. IV. The relation of oestrin to the luteal phase of the oestrus cycle. Parkes, A. S., Proc. Roy. Soc., London, **107**: 188. 1930.

In rabbits the prolonged injection of small amounts of oestrin (25 mouse units per day) caused no changes in the mammary glands of either the intact or recently ovariectomized immature rabbit. In a few of the rabbits a normal adult oestrus condition was produced in the uteri but no signs of pseudo-pregnancy were produced. When large amounts of oestrin (1200 m. u. per day) were injected into adult ovariectomized animals, the mammary glands developed but the growth was mainly of the ducts. During pseudo-pregnancy there was no effect produced by oestrin on the uterine and mammary changes. Injection of small amounts of oestrin (50 m. u. per day) into the anoestrus ferret produced only a slight development of the vulva and uterus. In the ovariectomized ferret, prolonged administration of oestrin leads to the appearance of normal oestrus changes in the uterus, vulva and vaginal epithelium. No changes characteristic of the luteal phase were produced by these injections.
—E. L.

A contribution to the knowledge of causes of sterility in male goats (Prispevek K Poznani Pricin Neplodnosti Kozlu). Podhradsky, J., Bull. de l'Ecole Superieure d'Agronomie, **17**: 1. 1930.

A 2-year-old buck was mated 40 times without impregnation. No sperm was deposited in the vagina. The genital organs, secondary sex characters, spermatogenesis, etc., were normal. The epididymis contained large accumulations, of cheesy consistency, which proved to be degenerated sperms. The epithelium was undergoing destruction, the duct was not obliterated. Sperm retention and ensuing sterility must have been due to some mechanical impediment. The author speaks of a tendency of sperm to produce coagulation.

—F. Gudernatsch.

The biologic significance of the female reproductive cycle. Novak, E., J. A. M. A. **96**: 2173. 1931. Abst., A. M. A.

The author states that the distinction made between the female sex cycle and the female reproductive cycle is a genuine one and not a mere play on words. A proper appreciation of the difference between these processes can be obtained only through a resort to the comparative method of study. The sex cycle in most of the lower animals, such as the rat or the mouse, is actually only a preparation for the sex act. The maximum of the development of the follicle coincides with estrus, the period of desire, at which coitus takes place. In other words, the extrusion of the ovum and the injection of the spermatozoa takes place at almost the same time, so that fertilization is the rule. Ovulation in these animals may therefore be looked on as actually a part of the sex act, and the estrus cycle as actually a sex cycle. Moreover, at the time of estrus, various other changes, such as dilatation of the vagina, are to be observed, all of them with a definitely purposeful relation to copulation. In the primates, however, as well as in some of the lower vertebrates, no such intimate association of ovulation with the sex act can be assumed. Certainly ovulation in the human female cannot be credited with any such sex significance as in the lower animals. While the sex cycle proper of the lower animals is complete at or shortly after ovulation and the period of estrus, this is certainly not the case with the menstrual cycle of women. After the follicular phase there follows a long developmental period of nearly two weeks, which proceeds parallel with the development of the corpus luteum in the ovary, and, as now believed, is due to the influence of the corpus luteum. During this luteal phase the endometrium advances steadily in its development and acquires those characteristics which are associated with the premenstrual or pregravid phase. Chief among these is the appearance of definite secretory activity in the glandular epithelium. Such changes are not found at any phase of the estrous cycle in the lower animals. They are, however, noted in these animals during pregnancy and in the interesting condition designated as pseudopregnancy. With the latter phenomena, best studied in the bitch, there take place in the genital canal a series of developmental changes exactly like those seen with actual pregnancy. In other words, there occurs a remarkable building up and preparation for the implantation and development of a fertilized egg which is not to arrive. The same elaborate preparation, equally futile in most instances, is to be seen in the endometrium of every woman of reproductive age in the pregravid phase of the menstrual cycle. Here, too, there is a constantly recurring preparedness, most often rendered useless by the failure of fertilization, so that the endometrium repeatedly dismantles itself through the desquamation of menstruation. The accompanying bleeding, i. e., menstruation, is merely an indication that fertilization and implantation have not occurred. It is this curious phenomena of pseudopregnancy, therefore, to which the human menstrual cycle must be compared, not only teleologically but also histologically and physiologically. The menstrual cycle, viewed in this light, is a reproductive cycle rather than a sex cycle. Perhaps it would be even more accurate to say that only in its follicular phase may it be considered as "sexual," though even here its primitive purposefulness has to a considerable extent been lost. The luteal phase, however, is concerned with pregnancy alone. While in former years there was much difference of opinion as to whether there is any basis of comparison between the estrus cycle of lower animals and the human menstrual cycle, there is no longer any reason to doubt their analogy.

Crystallographic description of theelin. Slawson, C. B., J. Biol. Chem. **87:** 373. 1930.

By the use of the polarizing microscope, the properties of this ovarian hormone have been determined. These properties include the indices of refraction and other data by which minute amounts of the hormone may be identified under the microscope.—Author's Abst.

Effect of estrin injections on the growth curve of young rats. Spencer, J., R. G. Gustavson and F. E. D'Amour, Proc. Soc. Exper. Biol. & Med. **28:** 500. 1931.

The growth rates of 12 young rats, each injected every second day with 40 units of a pure and carefully assayed preparation of estrin, were less than the growth rates of 12 litter mate controls. The gain in weight of the injected rats was 211% and that of the controls 262%. The weight of the testes of the injected male rats averaged only 29% and the weight of the ovaries of the injected females averaged only 43% of their corresponding controls. The ovaries of the injected females were pale and showed grossly no mature follicules or corpora lutea.—M. O. L.

The lipoid hormone of the hypophysis and the fertility hormones (L'hormone ipofisario lipoideo e la vitamina delle fertilita). Agnoli, R., Boll. d. Soc. ital. di biol. sper. **5:** 937. 1930.

The author studied in small mice kept on a diet of Mattil and Clayton the relations between the lack of vitamine E and the alcohol-ether soluble hormone of the anterior pituitary lobe. He found that the histological modifications of the male germinal and interstitial gland brought about by the diet of Mattil and Clayton are much ameliorated by an application of very small quantities of lipoidal hormone of the hypophysis. This is capable of stimulating the development of uterine muscle in a much more evident manner than prolan.—Author's Abst.

Anterior pituitary hormone in urine. A rapid method for the diagnosis of early pregnancy (Study of one hundred and seventy-five consecutive cases). Eberson, F. and M. H. Silverberg, J. A. M. A. **96:** 2176. 1931.

The Aschheim-Zondek test, modified by a new technic, has proved accurate and sensitive in the diagnosis of early pregnancy, including cases of ectopic gestation and missed and incomplete or complete abortion. The results in the series of 175 cases were free from error. An accurate and rapid method of differentiating pregnancy from conditions that simulate it is presented. Death of the fetus can be detected by this test in certain peculiar changes in the ovaries of rats viewed microscopically. These retrograde changes can be recognized and are diagnostic regardless of the misleading grossly positive appearance that may persist in the test animal as late as seven days after the death of the fetus in utero. The test has proved exceptionally valuable in medicolegal cases and is important in therapeutic abortion and in circumstances demanding a prompt diagnosis or exclusion of pregnancy. In the absence of macroscopic changes in the ovaries, the microscopic observations of peripheral organization of follicular cells and a peculiar vitreous alteration of the central mass of cells is diagnostic of very early pregnancy or its arrest. Despite the absence of luteinization, these structural and tinctorial changes noted in the follicular cells are specific and especially valuable in conditions that preclude diagnosis from the macroscopic observations alone. Further modification of this method indicates that the diagnosis of pregnancy can be made within thirty-six hours after obtaining a specimen of urine for the test. The accuracy of the test is not impaired by this new technic.—Authors' Summary.

On the cause of brain edema after pitressin. Barbour, H. G., G. E. Ellerbrook and M. W. Howard, Proc. Soc. Exper. Biol. & Med. **28:** 551. 1931.

Pitressin, added to blood in vivo or in vitro, diminishes post-mortal swelling of the normal brain. Pitressin probably disappears from the blood within 45 minutes after subcutaneous injection in rabbits, for brain swelling then becomes augmented. The brain edema previously demonstrated seems to result from the blood hydration which in turn is associated with anuria, and with loss of water from the skin.—Authors' Summary.

Findings in the hypophysis following ovarian irradiation. Borak, J. and F. Windhold, Klin. Wchnschr. **10**: 586. 1931.

The changes found in the pituitary gland of a 30-year-old woman, who had undergone intensive x-ray therapy of the ovaries, are described. In the ovaries the follicular apparatus was almost completely destroyed, while the interstitial cells were numerous. It appears that the destruction of the follicular apparatus alone was sufficient to produce changes in the anterior pituitary similar to the ones found after extirpation of the ovaries.—A. Rudy.

Comparison of the changes in the ovaries of immature mice and rats in the Zondek test (Les modification comparées de l'ovaire dans la réaction de Zondek chez la Souris et le Rat impubères).

The lipoids in the uterine epithelium and the "triad of oestrus" of immature mice and rats in the Zondek test (Les lipides de l'épithélium utérin et la triade oestrale dans la réaction de Zondek chez la Souris et le Rat impubères). Bourg, R., Compt. rend. Soc. de biol. **103**: 916; 918. 1930.

In both forms the maximum influence on the ovary occurs after about five daily injections of ½ cc. of urine from women in the first 4 months of pregnancy. In the mouse numerous haemorrhagic follicles and distended atritic follicles are the rule. In the rat these do not appear but instead a generalized hypertrophy of the theca interna of all types of follicles is the characteristic reaction. During oestrus, the Fallopian tube distends and becomes lined with cuboidal instead of columnar epithelium. The uterus is lined with actively proliferating cuboidal epithelium, from which has disappeared the fatty inclusions found in immature animals, while the vagina becomes dilated and covered with stratified epithelium. These changes referred to as the "triad of oestrous" are found in both rats and mice as the result of the urine injections and are probably dependent on the modifications of the ovary brought about by this procedure.—J. C. D.

The sexual function of the hypophysis (La fonction sexuelle de l'hypophyse). Brouha, L., Arch. internat. Physiol. **33**: 1. 1930.

The effects of castration can be corrected by grafts or by the injections of extracts. The removal of the anterior lobe of hypophysis results in a functional castration in spite of the presence of the sexual glands. The implantation of anterior lobes of the hypophysis from another animal corrects the disability in either a male or female. Extracts of the anterior lobe of the hypophysis made in neutral or acid medium, stimulate the sexual glands of both males and females, whereas the extracts made in alkaline medium stimulate the female but have no action on the male. Similar results were produced by extracts from the unrine, blood and placenta of pregnant females. Extracts having similar properties were prepared from the corpus luteum and the pineal by both acid and alkaline extraction.—E. L.

The action of the anterior pituitary hormone on the testicle with special reference to the interstitial cells (L'azione dell'ormone ipofisario ateriore sul testicolo, con particolare reguardo alle cellule interstiziali). Colombi, C., Boll. d. Soc. ital. di biol. sper. **5**: 726. 1930. Abst., Chem. Abst. **25**: 733.

The anterior pituitary hormone, when injected into mice in the form found in the urine of pregnant women, is active in causing a marked increase of interstitial substance. The increase is attributed to an hypertrophy of the prostate and of the seminal vesicles.

Metabolism and the hypophysis (Métabolisme de sommet et hypophyse). Chahovitch, X., Compt. rend. Soc. de biol. **103**: 330. 1930.

Seven rats received doses of pituitrin. Six showed reduction of their usual metabolism during activity and one no change. The basal metabolism also was lowered.—J. C. D.

Metabolic changes associated with pigmentary effector activity and pituitary removal in Xenopus Laevis.—I. Respiratory exchange. II. Calcium and magnesium content of the serum. Charles, E., Proc. Roy. Soc. London (B), **107**: 486. 1931.

The total respiratory exchange in air and the dermal oxygen consumption in water was determined in a series of Xenopus Laevis. (S. African clawed toad). The removal of the anterior lobe caused a lower oxygen consumption which the author attributes to the action upon the thyroid and ovaries. The rate of respiratory exchange is lowered by hypophysectomy, the effect on the pulmonary rate being greater than on the dermal rate. The respiratory quotient of the operated animal was higher than that of normal animals. The females had a higher contest of magnesium and calcium in the blood serum than males. Removal of either the anterior lobe or of both lobes of the pituitary caused a marked persistent fall in the calcium content of the blood serum.—E. L.

The effect of posterior pituitary extract upon the water economy of the frog (Über die Einwirkung von Hypophysenhinterlappenextrakten auf den Wasserhaushalt des Frosches). Heller, J., Arch. f. exper. Path. u. Pharmakol. **157**: 298. 1930. Abst., Chem. Absts. **25**: 4048.

Posterior pituitary extract causes an increase of weight in frogs, as high as 29% lasting 7-12 hours, owing to the retention of water in the liver, muscles, lymph channels, etc. Decerebration inhibits this pituitary effect. Frogs kept in 0.65% sodium chlorid increase as much as those kept in distilled water but the increase and subsequent return to normal are prolonged in time. Novasurol has a similar effect, while theophylline, thyroxine and the anterior pituitary extracts are ineffective.

The effect of the separated posterior pituitary hormone upon the water intake of frogs (Über die Wirkung der getrennten Hypophysenhinterlappenhormone auf die Wasseraufnahme beim Frosch). Heller, J., Arch. f. exper. Path. u. Pharmakol. **157**: 323. 1930. Abst., Chem. Absts. **25**: 4048.

Both the oxytocic and the vasopressor components of posterior pituitary extract cause an increase in the water retention of frog tissues, the former being comparatively stronger. The effect of the former is somewhat greater in summer frogs; that of the latter is independent of the season.

Thyrogenous dwarfism (myxoedema infantilis) in the domestic fowl. Landauer, W., Am. J. Anat. **43**: 1. 1929.

Report is made of a morphological and histological study of a dwarf Rhode Island Red pullet. The plumage of this bird appeared rugged, the skin and feathers were unusually dry. The upper beak was bent and there was a peculiar indentation between the base of the upper beak and the nasal and frontal bones. The eyes were relatively large and protruding. The tissue surrounding the eyes appeared swollen. There was a large oedematous swelling between the left eye and nostril. The tongue was quite abnormal: the posterior part swollen, the tip rolled under. In the long bones the perichondral bone appeared very compact (reduced number of Haverian canals), the endochondral bone was almost completely missing. The marrow cells were decreased in number. In the humerus the marrow was degenerated into connective tissue. The skull showed striking brachicephaly. The long bones and the pelvis also showed striking deviations in their proportions. The ovary was undifferentiated. The thyroid was enlarged and the greater part of the gland consisted of a plastic tissue without colloid, resembling Wegelin's struma diffusa parenchymatosa (microfollicularis). It is suggested that this dwarfism is analogous to human myxoedema infantilis. In an appendix skeletal measurements are given of 5 other specimens of the same type of dwarfism which essentially coincide with those reported for the original animal.

—Author's Abst.

The Laurence-Biedl syndrome: Report of a case. Rowe, S. N., Arch. Neurol. & Psychiat. **25**: 898. 1931.

The author reports the case of a white woman of 37 showing a pituitary type of obesity, retinitis pigmentosa, relatively immature external genitalia, and a mental age of 5 years (the Laurence-Biedl Syndrome), associated with

hypertension, a right hemiplegia, and hyperglycemia. The patient's brother is blind and has extra digits on each extremity but could not be persuaded to come to the hospital for study.—Author's Abst.

A highly potent liver extract for injection (Ein Hochwirksamer, Injizierbarer Leberextrakt). Gänsslen, M., Klin., Wchnschr. **9**: 2099. 1930.

The author reports, without details of method of preparation, the extraction of a protein-free liver extract which is successful in the treatment of pernicious anaemia. Two cc. of extract derived from 5 grams of fresh liver was given daily by intragluteal injections with effects comparable to the oral administration of 300-600 grams liver. The extract has been used with uniform success in over 40 cases of pernicious anaemia, of which 2 cases are given as examples. In most cases the use of the extract resulted in an increase in weight and in several in an improvement in the nervous disorders. The extract was able to restore the blood picture in certain cases of secondary anaemia, though its action was less rapid than in pernicious anaemia. There was a great decrease in the liver glycogen and a "heparin-like" action on the clotting time of the blood in injected animals. It further greatly mitigated the severity of bartonella anaemia in rats.—G. P. Wright.

Experimental and clinical studies on the peroral treatment of diabetes. II. The effect of liver on the carbohydrate tolerance. Gutmann, K. and S. Horawitz, Klin. Wchnschr. **10**: 591. 1931.

Of 17 diabetics fed on liver, 4 showed improvement in carbohydrate tolerance, but in only one case could it be definitely attributed to the liver. In the remaining 13 cases the carbohydrate tolerance decreased with the increase in the amount of liver administered.—A. Rudy.

The kidney threshold for glucose in diabetic and non-diabetic persons. Glassberg, B. Y., J. Lab. & Clin. Med. **16**: 948. 1931.

Contrary to the generally accepted impression, the kidney threshold for glucose shows wide individual differences. It may be below 100 or above 250 mgm. % true blood glucose. It appears to be independent of age and sex. The kidney threshold for glucose is not fixed in any one person and may show marked shifts within the space of a few minutes. Glycosuria in the absence of other findings does not indicate a disturbance in carbohydrate metabolism. The diagnosis of diabetes mellitus cannot be made on the mere presence of sugar in the urine. It cannot always be made in the presence of high blood sugar and glycosuria. In order to prevent unjustified dietary limitation, careful study is required before making a diagnosis of diabetes mellitus. Life insurance companies may safely revise their requirements so as not to exclude indiscriminately, persons whose urine reveals a glycosuria.—Author's Summary.

Blood sugar response to intravenous insulin in normals and in diabetics. Collens, W. S. and H. G. Grayzel, Proc. Soc. Exper. Biol. & Med. **28**: 487. 1931.

Equivalent doses of insulin on the basis of body weight when administered intravenously, produce a much greater depression in the blood sugar level in diabetics than in normals. This seems to indicate the absence of any substance in the blood of diabetics which might inhibit insulin action.

—Authors' Summary.

"Insulin-like" action of bean decoction. Liass, M. and V. Vovsi, Klin. med. **8**: 1190. 1930. Abst., J. A. M. A. **96**: 1746.

Liass and Vovsi studied the action of a decoction of bean pods on the blood sugar of rabbits. Removed pods (by keeping beans in water) were moderately triturated and used for preparation of a decoction; the latter was passed through a gauze filter. Blood withdrawn from the auricular veins of the animals was examined half an hour, one hour and two, three and four hours, after the decoction had been administered with a gastric catheter. A dose of 5 cc. of the decoction given daily, or a dose of 10 cc. given at intervals of a day, induced a decrease of the blood sugar. The action was maximal between two and four hours. A dose of 10 cc. given daily sometimes changed the hypoglycemia into hyperglycemia. Large doses of the bean decoction proved to be toxic; thus, 20 cc. of a 10% decoction given by mouth, or 10 cc. given by the vein, caused death of the animal one or one and one-half hours later. On

pathologico-anatomic examination the liver appeared to be completely deprived of glycogen, but no morphologic changes were found. The authors stress that obviously the action of the bean decoction differs from that of insulin because it does not replace the insular apparatus of the pancreas.

Insulin. Some effects on normal rabbits protected from hypoglycemia by ingestion of dextrose. Loeb, R. F., E. G. Nichols and B. H. Paige, Arch. Int. Med. **48:** 70. 1931.

A comparative study was made of the effects of "small" and of "massive" doses of insulin in well-fed and previously starved normal adult rabbits protected from hypoglycemia by the ingestion of large amounts of dextrose. The marked variation in the blood sugar curves of rabbits receiving identical treatment is emphasized. Massive doses of insulin do not have a greater effect on the hyperglycemia resulting from administration of dextrose than do small doses. Evidence is presented which suggests that in well-fed rabbits massive doses of insulin have not only relatively but actually less effect on hyperglycemia than do small doses. The storage of glycogen in the liver is suppressed by insulin in spite of the presence of persistent and marked hyperglycemia. In contrast to observations made in the presence of hypoglycemia, no definite histologic changes are found in the adrenal glands of rabbits protected from insulin shock by dextrose. This suggests that the changes observed by other investigators were associated with hypoglycemia, and were not due to the action of insulin per se. The injection of from 300 to 500 clinical units of insulin produces no general "toxic" effect in normal rabbits.

—Authors' Summary.

Innocent Glycosuria. Powelson, H. C. and R. M. Wilder, J. A. M. A. **96:** 1562. 1931. Abst., A. M. A.

The authors present the results of a study of 91 cases in which benign glycosuria was diagnosed on the basis of the response to the simple oral dextrose tolerance test. The patient reported for the test after a fast of from twelve to sixteen hours, having received adequate carbohydrate previously. One hundred grams of dextrose was given by mouth, with 500 cc. of water. Samples of urine and venous blood were taken before, and one-half hour, 2 hours and 3 hours after the dextrose was given. The determinations of blood sugar were made with the technic of Folin and Wu. The urine was tested with qualitative Benedict's solution. It was found that benign glycosuria presents no definite symptoms, and many cases probably escape detection. Normoglycemic glycosuria is by no means uncommon. Patients with benign glycosuria lose weight and strength when placed on treatment for diabetes. They gain in weight and strength when dietary restrictions are removed. They may be made very uncomfortable by treatment with insulin. On the other hand, true diabetes mellitus should be recognized early and treated appropriately in order to suspend its normal tendency to progression. The simple dextrose tolerance test described is a reliable procedure for differentiating normoglycemic glycosuria from early or mild diabetes mellitus. Of 82 cases diagnosed normoglycemic glycosuria by this test, diabetes mellitus did not develop in any in the intervals of one to twelve years that elapsed after the tests were made. The familial character of normoglycemic glycosuria is illustrated by a family in which the mother and 4 of 6 children were shown to have the disorder. Cases of alimentary hyperglycemia and cases of "diabetes innocens" should be treated as diabetes mellitus until they have been proved innocent by long observation. Cases of glycosuria of pregnancy are usually instances of normoglycemic glycosuria, but the prognosis in these is not certainly favorable. Cases of glycosuria accompanying furunculosis and other sapremic conditions may be innocent but their benign character is doubtful until it is proved to be so by later tolerance tests. True diabetes mellitus may be accompanied by a low renal threshold, which adds considerably to the difficulties of treatment.

Insulin diminution of normal vagus action (Über die durch das Insulin verursachte Verminderung des Varuseffecktes auf das Herz). Räiha, C. E. and P. Malm, Skandinav. Arch. f. Physiol. **61:** 64. 1931. Abst., Physiol. Absts. **16:** 46.

Experiments were made on rabbits, taking electrocardiographic records. The effect of a given electrical stimulation of the peripheral end of the right vagus was determined before and after insulin. It was concluded that the

diminished vagus effect seen after insulin is due to diminished response of the heart to vagus impulses rather than to "pseudoparalysis" of the nerve. There is a suggestion that the inhibitory effect of insulin on vagus activity is related to an increased potassium content of the heart.

The variations of glycogen in the liver and muscles immediately following injection of insulin in normal dogs (Les variations précoces du glycogène hépatique et musculaire chez le Chien normal sous l'influence de l'insuline). Rathery, F., R. Kourilsky and Mlle. S. Gibert, Compt. rend. Soc. de biol. **103:** 307. 1930.

Twelve dogs were studied for the glycogen changes in the liver and 7 for that in the muscles. The examinations were made from ten minutes to two and three-quarters hours after the injections. The liver glycogen fell rapidly, regularly, and to a marked degree. The glycogen in the muscles usually fell slightly but frequently there was no measurable reduction.—J. C. D.

Carbon monoxide diabetes—report on case. Rogers, H., California & West Med. **34:** 411. 1931.

The patient described was a white male of 35 who, on Dec. 5, 1921, was overcome by the exhaust gases of a truck and was removed to a hospital where glycosuria and hyperglycemia were discovered as well as carbon monoxyhaemoglobin in the blood. He received the proper dietary and insulin therapy in the hospital over a period of four weeks. When the author first saw the patient on Jan. 25, 1930, he was complaining of sudden attacks of amblyopia, nausea, vertigo, and headache. The duration of these attacks was from a few minutes to an hour. The family history was negative. Glycosuria was present, blood sugar was 101 mgm./100 cc. The author concludes that it is possible that the diabetes arose out of the poisoning by carbon monoxide gas.—I. B.

Abolishing coma in diabetes and its treatment if present. Ross, F. E., Pennsylvania M. J. **34:** 365. 1931.

To rob diabetes of coma would eliminate the terror of this disease, particularly in childhood. The prevention of coma is therefore the major consideration. Failure of the body, aided or unaided, to restore the normal acid-base balance results in a condition recently described by Atchley as "medical shock." This is characterized by vasomotor paralysis, manifested by rapidly lowering blood pressure, rapid and weakening pulse, anuria, and early dissolution. The menace of acidosis and coma in a case of diabetes is due to the fact that in this disease there is present, especially in children, a lessened ability on the part of the system to utilize fat. The prevention of coma in a diabetic child is a much greater problem than in the case of an adult on account of the metabolic demands of the growing organism. The balance in childhood is easily disturbed and things happen very quickly. Children are very susceptible to acute infections and an otherwise simple cold, or the onset of an attack of tonsillitis, may convert a mild case of diabetes into a severe case of coma. In ambulatory children an attack of acidosis frequently occurs after overindulgence in candy. Carbohydrates should not be suddenly withdrawn. Fats should be kept low. Reduction in proteins should be made cautiously. If a maintenance diet is not tolerated we must have recourse to insulin. As soon as a diagnosis of coma is made, insulin must be administered and the dosage can be approximately estimated if the percentage of blood sugar is known. Otherwise it is well to inject glucose simultaneously with the insulin in an amount approximating one gram to each unit of insulin and on a basis of 50 units for an adult. Other associated treatment must be administered in accordance with known principles and existing indications. In cases that do not respond to treatment despite heroic measures, blood transfusions may be of service.—I. B.

On the mechanism of insulin action (Über den Mechanismus der Insulinwirkung). Schmidt, A. A., Arch. f. exper. Path. u. Pharmakol. **153:** 79. 1930.

The leg vessels of dogs were prepared under ether-morphin anesthesia and ½, 1 and 1½ hours later blood samples were drawn from artery and vein. Blood sugar was determined by the method of Hagedorn and Jensen. Insulin (3 units per kgm.) was injected intravenously and further blood samples col-

lected at frequent intervals; on an average, in 8 experiments, the arterio-venous blood sugar difference rose from 1-2 mgm. to 7-11 mgm. % within 1 hour. Intravenous injection of salt solution had no effect on the a.v. blood sugar difference. In another group of experiments blood was obtained during continued ether-morphin anesthesia. Hepatic vein blood contained rather more sugar than portal blood after injection of insulin and the femoral artery femoral vein blood sugar difference was not significantly changed.—G. T. Cori.

The intranasal application of insulin (Über die endonasale Applikation des Insulins). Wassermeyer, H. and A. Schäfer, Med. Klin. **26**: 474. 1930.

The authors used dried insulin which was snuffed up into the nose, 10-20-50-100 units. The blood sugar was observed for 4 hours. They conclude that the action of insulin thus used is limited. Raising the dosage did not increase the fall of blood sugar any more than did small doses. The authors tried to use it merely for the milder cases of diabetes and consider it merely an experimental problem.—H. J. J.

Parathormone dosage and serum calcium and phosphorus in experimental hyperparathyroidism leading to osteitis fibrosa. Bodansky, A. and H. L. Jaffe, J. Exper. Med. **53**: 591. 1931.

The bone lesions of chronic hyperparathyroidism presented the essential features of osteitis fibrosa cystica (von Recklinghausen's disease) in varying degrees of severity, depending on the parathormone dose, the calcium intake, and the duration of the treatment. Young dogs were used because the bone changes are more easily demonstrated in actively growing animals. Low calcium intakes permitted the use of large doses of parathormone for long periods without fatal hypercalcemia and without symptoms of overdosage, and led to the development of the most marked lesions. Early in the treatment, when the puppies were about 2 months old, parathormone caused a more marked relative rise of serum calcium than in normal adult dogs. On a low calcium intake hypercalcemia tended to disappear on parathormone doses eventually as large as 6 units per kgm., apparently due to the reduction of a readily available calcium reserve; but when either the calcium intake or the daily dose of parathormone was increased, a rise of serum calcium and symptoms of overdosage developed. Hypocalcemia developed finally on a low calcium diet. tetany occurring at a calcium level which was higher and a phosphorus level which was lower than in tetania parathyreopriva of young puppies; about 0.1 gm. of calcium daily was apparently sufficient to prevent hypocalcemia. The serum phosphorus in chronic hyperparathyroidism in young puppies continued at or rose above the high level observed in normal young animals. Toward the end of long periods of treatment with large parathormone doses (about 5 units per kgm.) serum phosphorus approached normal levels, pronounced hypercalcemia was absent, but hypotonia and other symptoms of hyperparathyroidism were present. The data obtained during prolonged periods of treatment with parathormone indicate tolerance due to some compensation rather than immunity.—A. Bodansky.

Studies on parathyroidectomy syndrome. III. Its course in animals under strontium and calcium treatment. Comel, M., Boll. d. Soc. ital. di biol. sper. **5**: 729. 1930.

IV. The effect of irradiated ergosterol administered in excessive doses and its mechanism. Ibid. 732. Abst., Chem. Absts. **25**: 742.

In the parathyroidectomized animal treated with toxic doses of strontium, it is possible to impede tetany but not the picture of the parathyroidectomy syndrome, which eventually results in the death of the animal in marasma and cachexia. The antitetanic action of strontium is different from that of calcium and has its seat in the nervous system. Irradiated ergosterol in large doses, 0.5-0.7 million rat units, administered to parathyroidectomized dogs impedes the onset of tetany and other functional symptoms characteristic of parathyroid insufficiency. However, there are no marked serological changes; it does not prevent hypocalcemia. There is some increase in blood P so that the ratio Ca/P is not lowered to the level common to tetany. Later, the hypocalcemia disappears rather quickly and the blood Ca becomes normal. Simultaneously, the blood P also decreases and the ratio Ca/P becomes normal. This behavior is attributed to the presence of accessory parathyroid tissue and to the formation of compensating factors.

The preservation of the parathyroids in goiter surgery. Curtis, G. M., Illinois M. J. **49**: 361. 1931.

The preservation of the parathyroid glands in goiter surgery calls for a knowledge of their position and their blood supply. Four glands are ordinarily present, of a brownish-yellow color, and lying, as a rule, between the medial surface of the lateral lobe and the trachea and esophagus but more frequently toward the lower pole of the thyroid gland. Each receives an individual artery, usually arising from the inferior thyroid arteries or their branches. Through the branches from which they arise, there is an abundant collateral blood supply from the other thyroid arteries of the same and opposite sides, from the arteries of the pharynx and esophagus, from those of the larynx and trachea, from surrounding muscular branches, and from branches in the deep cervical fascia. The preservation of the collateral supply is best effected by leaving the posterior and medical capsule, as well as the posterior isthmus in situ, and avoiding tugging on the gland in the luxation necessary to subtotal resection. Aberrant parathyroids are best preserved by leaving behind so much of the lateral and inferior polar fascia and capsule as possible.—I. B.

The calcium content of the skeletal muscles after thyroparathyroidectomy and parahormone injection. Hsu, F. Y. and C. Tsai, Chinese J. Physiol. **4**: 423. 1930. Abst., Chem. Absts. **25**: 733.

Thyroparathyroidectomy resulted in a drop in the calcium content of the muscles of dogs. This drop was less abrupt and less extensive than the fall of serum calcium. This suggested that the diminution in the muscle was the result of the drop in the blood. The effect of parahormone administration was variable, but in no case did a depression of muscle calcium result. In general the muscle calcium followed the serum calcium.

Effects of ligature of inferior thyroid artery on calcemia and functional symptoms in ankylosis (Des effects de la ligature d'une des arteres thyroïdiennes inférieures sur la calcémie et la symptomatologie fonctionnelle dans un cas de polyarthrite ankylosante). Leriche, R. and A. Jung, Bull. et mém. Soc. nat. de chir. **56**: 1249. 1930. Abst., J. A. M. A. **96**: 564.

Leriche and Jung report a case of multiple ankylosis of 12 years' standing. The spinal column was completely rigid; only the slightest movements of rotation and flexion of the head were possible. The ankylosis had affected other articulations also for 2 years and the patient was almost unable to move at all and had intense pain. Since hypercalcemia was present, the authors decided on parathyroidectomy. They removed a small body on each side, believing them to be the inferior parathyroids. One of the fragments, however, was merely a bit of fatty tissue. Immediately after the operation the patient showed a marked improvement: the pain disappeared and he was able to move his arms, to turn himself in bed, and finally to stand erect. The calcemia was reduced from 0.116 to about 0.09 grams. Six weeks later, however, the ankylosis set in again and the patient gradually returned to his former condition, although the calcemia remained normal. The authors feel that the unfavorable developments in this case are not so discouraging as they appear at first because of the long duration of the disease. They consider it encouraging that any amelioration should have been produced. This case illustrates the extreme difficulty of identifying the parathyroids. The authors report a second case in which the ankylosis had begun 5 months earlier. Before attempting to identify and isolate the parathyroids they divided the inferior parathyroids. Although the fragment that they removed, as in the first case, did not prove to be parathyroid, the ligatures served to decrease the glandular secretion and the patient's condition was immediately improved. The calcemia was lowered, the pain disappeared and, wherever the ankylosis was not complete, mobility of the joints was restored. The amelioration has persisted for 4 months. The authors feel that this case demonstrates the efficacy of parathyroid operations performed sufficiently early in the development of the disease.

Action of viosterol and parathormone in thyroparathyroidectomized dogs. Spies, J. W., R. H. Wilson and J. A. Stringham, Proc. Soc. Exper. Biol. & Med. **28**: 529. 1931.

In thyroparathyroidectomized dogs suitable doses of either viosterol or parathormone will cause a rise in the level of the blood serum calcium, which

is remarkably parallel to that of the electrical reaction figures, and, to a lesser extent, that of the urinary calcium excretion values. The elimination of calcium by way of the feces is apparently increased during the administration of parathormone and is decreased during that of viosterol, thus tending to produce a negative calcium balance in the former and a positive one in the latter instance.—Authors' Summary.

The effect of thyroparathyroidectomy and parahormone administration on gastric motility in dogs. Tsai, C., Chinese J. Physiol. **4**: 415. 1930. Abst., Chem. Absts **25**: 733.

After parathyroidectomy in dogs the stomach no longer exhibits hunger contractions, despite several days of deprivation of food, and gastric tone is permanently lowered. Administration of parahormone to normal dogs has no effect on gastric motility except a partial and temporary inhibition. With parathyroidectomized dogs it restores the gastric tone but not the appetite.

Treatment of severe forms of progressive chronic deforming rheumatism by parathyroid extract (Traitement de certaines formes graves du rhumatisme chronique déformant progressif par les extraits' parathyroïdiens). Weissenbach, R. F., F. Françon, L. Perlés, and P. Seidmann, Bull. et mém. Soc. méd. d. hôp. de Paris, **54**: 1843. 1930. Abst., J. A. M. A. **96**: 984.

The authors report a case of progressive chronic deforming rheumatism in which subcutaneous injections of parathyroid extract were used with good results. They have used this treatment successfully in about ten cases. The immediate results of the treatment, which manifest themselves after the first few injections, consisted of articular flexibility, increased facility of movement, and a feeling of well being. The amelioration appeared in from twenty to thirty minutes after the injection, lasted for about twelve hours and then disappeared. The authors point out that this temporary amelioration, which often permits a patient to resume an apparently normal life, is similar to the effects of insulin in diabetes. The late and cumulative effects of the injections of parathyroid extract are also noteworthy; continued use of the treatment tends to relieve permanently the stiffness of the joints and to permit greater ease of movement. While the treatment is, of course, useless for extreme cachexia and deformity, it is valuable in long standing cases like the one reported in which exact mechanism of the therapeutic effects of the parathyroid extract is not yet known. Since the treatment is so simple, however, and involves no risk if the patient is given careful attention, the authors recommend its use in refractory cases.

Effect of single intravenous injections of thyroxine before and after thyroidectomy. Boothby, W. M. and C. M. Wilhelmj, Proc. Staff meet., Mayo Clinic, **6**: 251. 1931. Also Am. J. Physiol. **97**: 506. 1931.

The extra heat produced by 10 mgm. thyroxine during the first seven days following its intravenous injection before thyroidectomy averaged 300 calories for three experiments without iodine and 311 calories for two experiments with iodine. Subsequent to these experiments the dog was thyroidectomized and the extra heat following 8 injections of the same amount of thyroxine averaged 616 calories. Therefore the calorigenic action of a single intravenous dose before thyroidectomy is the same whether iodine is or is not administered before and during the experiment. On the other hand, removal of the thyroid nearly doubles the calorigenic action of thyroxine.—W. M. Boothby.

The effect of hypothyroidism on gastric and intestinal function. Brown, T. R., J. A. M. A. **97**: 511. 1931. Abst., A. M. A.

From the study of a group of cases with lowered basal metabolic readings, a few cases of frank myxedema, or at least of the forme fruste, and a number of cases with readings lower than is usually regarded as a low normal reading, the author draws the following conclusions: (1) There is no characteristic gastro-intestinal picture presented by this group of cases, the digestive symptoms, gastric or intestinal, being purely functional in nature and not at all different from those encountered in a variety of other conditions. (2) It is evident, however, that hypothyroidism, especially if the readings are very low,

plays a considerable part in certain cases of intractable constipation not corrected by the usual means, which are not infrequently observed in women in the late forties or fifties; the incidence of hypothyroidism in such cases is shown by the marked success in regard to these symptoms under proper dosage of thyroid extract. As regards the gastric secretory condition in those cases with relatively slight basal reductions, that is, with readings between minus 10 and minus 20, the readings are quite normal, and there is no difference between these readings and those obtained in normal individuals; that is, those with readings from minus 10 to plus 10. On the other hand, in the cases with very low readings, minus 20 and below, there was a marked tendency to gastric subacidity, a considerable portion of the cases presenting achlorhydria. (3) In the cases of intractable constipation, especially in women in the forties and fifties, it is advisable to consider the possibility of an unrecognized hypothyroidism playing a part in the picture, which can be relatively easily determined by careful basal metabolic readings and by the effect of therapy with thyroid extract if the readings are low.

The heart in goitre. Chesky, V. E., Am. J. Surg. **7**: 27. 1929.

This is a short article reviewing 200 consecutive case histories of patients operated upon for goitre. Thyroid toxemia, if acting sufficiently long, always produces cardiac symptoms and eventually serious heart damage. There is no definite cardiac pathology directly attributable to thyroid toxemia. Undamaged hearts in young individuals bear thyroid toxemia exceedingly well. Thyroid toxemia frequently produces cardiac arrhythmias, auricular fibrillation being the one most frequently seen. Toxemia developing in long-standing colloid goiters produces a clinical picture in which the cardiac symptoms completely overshadow the other symptoms of toxemia. There are 3 types of patients with goiter and cardiac symptoms and findings, namely, neurocirculatory asthenia, hypertension cases and those with myocarditis, in which the goiter is only incidental and in whom thyroidectomy is definitely contraindicated.—W. D. Reid.

Geographic location and the iodine content of the thyroid gland. Fenger, F., R. H. Andrew and J. J. Vollertsen, J. Am. Chem. Soc. **53**: 237. 1931.

This work was carried out to determine the iodine content and physiological function of the thyroid gland of domestic animals in the northern and southern portions of the United States. One-pound samples of hog thyroid glands were collected once a week at West Fargo, North Dakota (47° north latitude) and at Forth Worth, Texas (33° north latitude) over a period of one year, from January, 1929, to January, 1930. It was found that the seasonal variation in the iodine content is most pronounced in the northern glands. The yearly average for desiccated and defatted hog thyroid glands from North Dakota is 0.32% of iodine, with a top peak of 0.53% in August and a low dip down to 0.13% early in March, while that of the Texas glands is 0.60% iodine, with a maximum of 0.78% in August and a minimum of 0.44% in the latter part of February. The high iodine level of the Texas glands and the greater seasonal fluctuations of the North Dakota thyroids are attributed to the geographic location of the two states.—Authors' Abst.

Action of sodium fluoride on the basal metabolism of the rat (Action du fluorure de sodium sur le métabolisme basal du rat). Goldenberg, L., J. de physiol. et de pathol. gén. **28**: 558. 1930.

Slow intoxication of rats, dogs and fowls with sodium fluoride results in an obvious hypertrophy of the thyroid gland (dilatation of vesicles and hypertrophy of connective tissue) and in an absence of further growth of young animals. Metabolic measurements after administration of sodium fluoride were interesting. A Haldane apparatus modified by Danoff was used. About twenty-five rats were studied before and after fluoride intoxication. Oral administration of low doses requires a long time to show its action on metabolism, but intraperitoneal injection of 15 to 18 mgm. NaFl. per kgm. in 1% aqueous solution induces a quick lowering (—12 to —63%) of the basel metabolic rate. This effect may last for hours and even for a few days. Lower doses have an inconstant effect.—Z. M. Bacq.

Mental derangements in hypothyroidism. Their misleading effects in diagnosis. Hayward, E .P. and A. H. Woods, J. A. M. A. **97**: 164. 1931.

The authors assert that insufficiency of thyroid secretion sometimes shows its most striking effects through malfunctioning of the brain cells. The patient may become depressed and apprehensive, thought may become slow and bodily movements retarded. The condition is easily mistaken for a depressed psychosis. Or there may be irritability and excitement leading to the diagnosis of mania. Patients may show thought distortion with hallucinations and delusions, which may become so bizarre as to be interpreted as signs of dementia praecox. In these psychotic cases, even though the physical signs of myxedema are present, those signs are easily overlooked. This is partly because some physicians at once relegate patients who show mental derangement into a nimbus of mystery and infer that somatic disease cannot be expressed in mental symptomatology. A more excusable cause for overlooking evidence of physical disease is that the patient's mental attitude sometimes makes physical examination difficult or impossible. An illustrative case is described of a frank psychosis with schizoid coloring in a woman of 41 who showed various metabolic evidences of thyroid deficiency. Under thyroid medication the psychosis completely cleared up.—R. G. H.

Systematic reducing treatment with thyroxin. Hellfors, A., München. med. Wchnschr. **78**: 826. 1931.

On reinvestigation thyroxin has been found valuable in the treatment of obesity. In comparing the different brands of thyroxin on the market, an increase of 1% in the basal metabolic rate was produced by each in the following amounts: ¼ mgm. thyroxin Henning, 1 mgm. thyroxin Roche, 2 mgm. thyroxin Shering and 1 tablet thyreoidin Merck.—A Rudy.

Graves' constitution (Warthin). Hellwig, C. A., Surg. Gynec. & Obst. **52**: 43. 1931.

Sixty thyroid cases were studied clinically and anatomically with the object of determining whether Warthin's theory could be confirmed that in Graves' disease the thyroid gland is not the chief pathogenic factor, but an incidental complication to a constitutional thymicolymphatic anomaly. Of Hellwig's cases of Graves' disease and toxic goiter, only 66% had lymphoid tissue in the thyroid gland and of the cases without clinical symptoms of thyreotoxicosis, 38.5% showed lymphocytic infiltration. In typical cases of status thymicolymphaticus, on the other hand, no lymphoid tissue was found in the thyroid gland. The conclusion is reached from this study that lymphocytic infiltration of the thyroid gland is not a manifestation of an underlying constitutional anomaly, but is a purely local response to hyperplasia and hypersecretion of the gland.
—Author's Abst.

A case of ovarian carcinoma with metastases in the thyroid glands and Basedow's symptoms (Cas de carcinome de l'ovaire, avec métastases dans la thyroïde et symptomes de Basedow). Hoffmann, P., Bratisl. lekár. listy, **11**: 44. 1931.

The author describes an interesting case of ovarian carcinoma, which became metastatic in the thyroid gland and thus induced Basedowian symptoms.
—Author's Summary.

Common mistakes in the diagnosis and treatment of goiter. Jackson, A. S., Illinois M. J. **49**: 103. 1931.

This is a timely discourse on the many pitfalls which beset the diagnosis of thyroid disease in general practice. An attempt is made to discuss the better understood problems of diagnosis and classification. A few of the more important sources of error in diagnosis and treatment are presented. Particular emphasis is laid upon mistakes in diagnosis arising from failure to interpret properly the basal metabolic rates. The differential diagnosis of neurasthenia and hyperthyroidism is considered of importance. Hyperthyroidism in older persons simulating heart disease is frequently a perplexing diagnostic problem. Attention is called to "iodine fast," cases of exophthalmic goiter, and the danger of prolonged use of iodine.—I. B.

The influence of hyperthyroidization and thymization on the weight of mature birds (Ueber den Einfluss der Hyperthyreoidisation und der Hyperthymisation auf das Gewicht der Ausgewachsenen Voegel). Fifth contribution to the study of the thyroid-thymus antagonism during development. Krizenecky, J., Ztschr. f. vergl. Physiol. (Abt. C der Ztschr. f. wissensch. Biol.), **8**: 16. 1928.

In this and the 2 papers reviewed below, the author offers further contributions concerning the antagonistic influence of the thyroid and thymus on growth. Krizenecky had shown previously that feeding of thymus to pigeons would counteract the loss of weight caused by simultaneous thyroid feeding, while thymus feeding alone would exert an unfavorable influence on weight, though by no means as pronounced as the thyroid effect. A similar antagonism had been noted by Sklower (1927) on mice, and by Krizenecky and Pohradsky (1926) on tadpoles. The latter two observed that thyroid-fed tadpoles retarded in growth would grow normally, when thymus was applied with the thyroid. They consider this thymus action, which is antagonistic to thyroid, a specific one. It appears only when a state of hyperthyroidism exists and, thus, is of a regulative nature. The author has now observed the same antagonism in pigeons. Two sets of animals (January and May) were studied. A basal diet consisted of wheat, corn and water. The controls were given dried veal, the experimental animals dried thyroid, thymus, or both in ratios 1:2 (thyr. 1/6 g.) and 1:4 (thyr. ⅛ g.). The controls maintained their weights or gained slightly. The hyperthyroidized animals lost up to 46%, the hyperthymized lost slightly up to 6%. Thyroid + thymus in ratio 1:2 caused weight loss between 14 and 19%, thus considerably less than thyroid alone. Group 1:4 lost weight in the same manner as thyroid and died on the 8th day. In the second series (May) the controls showed a better gain, average 16%, the hyperthyroidized animals lost about 50% less than in series I. The average loss was 20%. The hyperthymized animals gained about 6% (i.e., less than the control). Thyroid + thymus, 1:2, lost slightly 15-18%, up to the 21st day, then remained stationary. Thus, in both series, thymus checked the weight loss produced by thyroid, less so in May than in January. According to Riddle, winter thyroids are more active than summer thyroids, and Krizenecky believes that these seasonal differences in the normal metabolism are responsible for the differences in experimental weight figures. The thymus can exert its antagonistic action only, when a state of hyperthyroidism exists. In 1926, Krizenecky and Pohradsky stated, on the strength of their tadpole experiments, that the antagonistic action of the thymus seems to be "activated" by the thyroid.—F. Gudernatsch.

Further experiments to determine the influence of hyperthyroidization and thymization on the weight of mature birds (Weitere Versuche ueber den Einfluss der Hyperthyreoidisation und der Hyperthymisation auf das Gewicht Erwachsener Voegel). Sixth contribution to the study of the thyroid-thymus antagonism during development. Krizenecky, J., Ztschr. f. vergl. Physiol. (Abt. C der Ztschr. f. wissensch. Biol.), **8**: 461. 1928.

Krizenecky has ascribed the differences in weight figures to differences in the inherent thyroid:thymus ratio, the winter pigeons being in a state of hyperthyroidism to begin with. In the present work he attempted to hyperthyroidize summer pigeons (June) and tested on these the antagonistic action of the thymus. The controls gained about 16%, the thyroid animals (¼ g. per animal per day) lost about 20%, the thymus animals gained 8%. Thyroid + thymus, 1:2, lost up to the 12th day 14% on the average, i.e., the loss is only half of that of thyroid alone. Experimental hyperthyroidism, thus, brought out the antagonistic action of the thymus. In the second series, the controls gained 19%, the thyroid animals (½ g.) lost up to 49% (corresponding to loss in winter experiment), the thymus animals gained 12%. Thyroid + thymus, 1:1, lost about 17%. Here, too, the thymus antagonized the weight loss produced by experimental hyperthyroidism in summer pigeons. The author restates his belief that the degree of thymus counteraction depends on the degree of thyroid action. Natural or induced hyperthyroidism stimulates the regulative activity of the thymus.—F. Gudernatsch.

Further experiments to determine the influence of hyperthyroidization and thymization on plumage growth of chicks (Weitere Untersuchungen ueber den Einfluss der Hyperthyreoidisierung und Hyperthymisierung auf den Befiederungsprozess bei den Huehnerkuecken). Eighth contribution to the study of the thyroid-thymus antagonism during development. Krizenecky, J. and M. Nevalonnyj, Arch. f. Entwcklngsmechn. d. Organ. (Abt. D d. Ztschr. f. wissench. Biol.), **115**: 876. 1929.

The authors offer further evidence for the influence of thyroid and thymus, when given per os, on plumage growth in domestic fowl. Thyroid causes acceleration, thymus retardation of the process. Italian partridges did not show it. To explain this difference, the authors assumed that the rapidity with which plumage growth advances in young Italian partridges cannot be increased by artificial stimulation, nor can it be counteracted. In the present experiments, hyperthyroidization and thymization on 3-day chicks prove the correctness of their assumption. After 11 days, differences in plumage length and density were noticeable, distinctly so on the 18th day. Controls were between thyroid and thymus-fed. Thyroid also produces the usual partial albinism and sexual dimorphism 10 days earlier than control and thymus; the thymus influence is strongest during the early period. Furthermore, thyroid chick plumage shows indications of feminization, or rather of an intersexual type. Plumage development thus seems to receive a directing stimulus, the strength and time of action of which depends on the thyroid-thymus interplay prevailing in the particular species or variety.—F. Gudernatsch.

Non-activated (apathetic) type of hyperthyroidism. Lahey, F. H., New England J. M. **204**: 747. 1931.

Patients suffering from this condition are almost the reverse in appearance and reactions of the typical hyperthyroid. Among other things, they do not show the high metabolic rate, the abnormal heart action, the exophthalmos, nor the goiter. These patients appear as good surgical risks but are actually the reverse. They are prone to go into coma and die quietly after apparently standing the thyroidectomy well. The author advises a two-step operation in all cases of the apathetic type.—J. C. D.

Late cardiac manifestations of toxic goiter. Luginbuhl, C. B., Am. J. Surg. **7**: 183. 1929.

An over-demonstrative heart is characteristic of the thyrotoxic patient, and is the most constant symptom of thyroid disease. This exaggerated response of the heart to even casual stimuli occurs early in thyrotoxic states. The severity of the heart symptoms, of which the patient himself is often painfully conscious, and the absence of demonstrable organic lesions are at striking variance. It must be determined: first, whether the heart lesion is of primary development and the goiter a coincidence; second, whether the cardiac lesion is a chance development in a patient already afflicted with goiter; or, third, whether the cardiac lesion is secondary to thyroid disease. The cardiac symptoms may be: of mechanical origin, of toxic origin, or due to both factors. Luginbuhl cites the work of Takane, who by the administration of iodine compounds, was able to produce pathologic changes in the heart similar to those he had observed at necropsy. Takane concluded that acute myocarditis resulted because iodine compounds were disintegrated by the lactic acid in the heart muscle, and the resulting chemicals were irritative in their effect. Goiter heart developing in a patient who has long had a so-called silent goiter, or who has a hyperfunctioning rather than a grossly enlarged thyroid is overlooked by many, even by most physicians. The rate of the basal metabolism is often only slightly or not at all increased. Luginbuhl is not convinced that arterial hypertension, and the diseased thyroid and goiter heart necessarily bear a cause and effect relationship to each other. Some of the so-called goiter deaths following operations are in reality heart deaths, pure and simple: a coronary accident is a coronary accident though it occur in a goiter patient. The treatment should be individual in character. Luginbuhl reminds us of the over-optimistic or over-timorous internist and the overzealous surgeon who rushes these patients to the operating table, with insufficient preparation. Every goiter patient, and particularly every one with cardiac disturbance, should be under the observation and directions of a competent internist, not because these patients are medical but because they are not properly surgical until medical treatment has made surgery relatively safe. Rest in bed is uni-

versally applicable to the goiter patient with a cardiac lesion, but one should extend this to securing rest in bed. Sedation by a barbital preparation is desirable. The response to digitalis is erratic and not readily predictable. Quinidine, when indicated, has never given rise to dangerous effects in Luginbuhl's cases. The prognosis of these cardiac cases should be guarded. With judgment and care, the operative mortality will be low, but the extent to which the individual heart will "come back" following operation cannot be accurately foretold.—W. D. Reid.

Studies on goiter produced by cabbage. McCarrison, R., Indian J. M. Research. **18**: 1311. 1931. Abst., J. A. M. A. **97**: 352.

The purpose of McCarrison's investigation was threefold; to observe on rabbits the goiter-producing action of cabbage; to study the changes in iodine metabolism, as evidenced in the gland itself and in the urinary excretion of iodine, that might be brought about by the goitrogenic agent in cabbage; and to discover substances antagonistic to this agent. It was found that cabbage contained a potent goitrogenic agent. The goiter-producing potency varied at different seasons of the year; it was greatest in the autumn, least in midsummer and of intermediate degree in the early summer months. Steaming augmented the goiter-producing potency in one experiment and reduced it in another. Carrots, sprouted Bengal gram (legume) and freshly cut green grass appeared to possess antigoitrogenic properties though these were not of a high order. Both bran and sodium chloride augmented the goitrogenic potency of steamed cabbage. Viosterol enhanced the goitrogenic action of steamed cabbage, its action in this regard was uniform. The soaking of steamed cabbage in fresh chlorine water neither favored nor disfavored the goitrogenic action of the cabbage, though it caused the iodine content of the thyroid to be low and the urinary excretion of iodine to be high; its action in these regards was fairly uniform. Thyroxine exerted a definite antigoitrogenic action more marked in degree but less uniform than that of iodine. Iodine exerted a definite antigoitrogenic action, less marked in degree but more uniform than that of thyroxine. Manganese chloride exerted a definite antigoitrogenic action equal in uniformity to that of thyroxine and in degree to that of thymol. Thymol exerted a definite antigoitrogenic action which, though less uniform than that of manganese chloride was, in the mean, equal to it in degree. The iodine content of the goitrous thyroid was in inverse relation to its size. The urinary excretion of iodine was in inverse relation to the size of the goitrous thyroid.

Study of the morbid anatomy of hearts from patients dying with hyperthyroidism. McEachern, D. and G. Rake, Johns Hopkins Hosp. Bull. **48**: 273. 1931.

The authors review the literature on the macroscopic and microscopic changes found in the heart of patients dying with hyperthyroidism. They point out the contradictions of the evidence and the lack of studies on a control series of hearts. Twenty-seven cases of patients dying with hyperthyroidism are reported with clinical and pathological findings; the morphological cardiac findings in these are compared with those in 150 control cases. In 14 instances the hearts were normal; in 8 there were mild degrees of fibrosis and slight cell infiltration resembling changes found in the control series; in 5 cases there were marked changes, but of these 3 showed co-existent (rheumatic or syphilitic) heart disease. There was no relationship between auricular fibrillation or the duration of hyperthyroidism and the degree of change demonstrable in the heart. The authors believe that the changes in the "hyperthyroid heart" differ only quantitatively, not qualitatively, from the changes in so-called normal hearts, especially if these be chosen from the same decade of life, and that it is impossible to ascribe the cardiac phenomena of the disease to structural changes in the muscle.—G. W. Rake.

Thyroidectomy for thyrotoxicosis in patients beyond the fiftieth year. Mora, J. M. and E. I. Greene, Illinois M. J. **49**: 338. 1931.

This report deals with a study of 200 thyrotoxic patients at least 50 years old, who were subjected to thyroidectomy. Of these, 133 (66.5%) were of the hyperplastic variety, while 67 (33.5%) were cases of toxic adenoma. Without exception there was a definite response to iodine in every case. Of the 200 cases studied postoperatively, the operative mortality rate was 3% Postoper-

ative hypothyroidism was noted in 64 patients, while in 5 there occurred mild temporary tetany, in 6 there was temporary postoperative recurrent laryngeal nerve trauma, in 2 of which the damage persisted.—I. B.

A comparison of the influence of iodized milk and of potassium iodide administered directly, on the size and iodine content of the thyroid gland of rats. Krauss, W. E. and C. F. Monroe, J. Biol. Chem. **89**: 581. 1930.

Iodized milk, produced by feeding cows KI, was compared with normal milk and direct KI additions to normal milk as to effect on the size and iodine content of the thyroid gland of rats. Three prophylactic trials, involving 71 rats, were conducted. The use of a basal ration was avoided by feeding exclusive milk diets properly supplemented with Cu and Fe to avoid anemia. Curative data were made possible through the use of a special basal ration which had been found to cause enlargement of the thyroid gland. Whenever iodized milk or KI was fed the thyroid gland was reduced in size and its iodine content was increased, the magnitude of the change in each case being approximately proportional to the amount of iodine fed. It was concluded that the iodine in iodized milk exerts as great an influence on the size and iodine content of the thyroid gland of rats as does an equivalent amount of iodine administered directly or added to normal milk. A brief discussion of the advantages and disadvantages of an iodized milk supply is included.—W. E. Krauss.

Experimental hyperthyroidism and its effect upon the myocardium in guinea pigs and rabbits. Rake, G. and D. McEachern, J. Exper. Med. **54**: 23. 1931.

A study was made of the pathological changes in the hearts and other tissues of 44 rabbits and 17 guinea pigs rendered hyperthyroid with thyroxine. Tissues from 43 normal rabbits and 20 normal guinea pigs were examined as a control. The microscopic changes in the heart and other tissues of hyperthyroid animals were shown to be insignificant and to vary but little and that only in degree from changes seen in the control animals. In agreement with their investigation of human material, the authors believe that hyperthyroidism per se produces no specific lesion in the heart, but may accentuate the damage produced on the one hand by physiological wear and tear and on the other by any coincidental infection or other disease.—G. W. Rake.

Studies in thrombo-angiitis obliterans (Buerger). VIII. Effect of thyroid administration on blood volume. Silbert, S. and Mae Friedlander, J. A. M. A. **97**: 17. 1931.

Fourteen typical cases of thrombo-angiitis obliterans were treated with thyroid extract over periods of from four to eight months. Determinations were made at monthly intervals of the basal metabolism, chemical composition of the blood and clinical condition. Following administration of thyroid the low blood volume promptly increased to normal but fell slowly as the drug was continued. On withdrawal of the drug, the blood volume returned to the low figure first obtained. With increase in blood volume, the total proteins, calcium and cholesterol figures diminished to normal and again increased when thyroid was withdrawn. The low blood volume in cases of thrombo-angiitis obliterans can be raised to normal by administration of thyroid.

—Authors' Summary.

Etiology of Graves' disease. Sloan, E. P., Am. J. Surg. **7**: 194. 1928.

This is a review of the current ideas on the etiology of exophthalmic goiter with a presentation of the author's own views. He believes the cause of Graves' disease to reside in the thyroid gland, the organ becoming disturbed from inflammation or from infection. Other phenomena commonly present in Graves' syndrome and ordinarily assignable to the vegetative nervous system and the system of ductless glands are regarded by Sloan as events secondary to thyroid dysfunction.—I. B.

Enlargement of thyroid gland in children. A study of 100 cases of so-called goiter. Topper, A. and H. Mulier, Am. J. Dis. Child. **40**: 674. 1930.

In a study of 100 cases of thyroid enlargement in children between 6 and 14 years of age, the authors found the incidence of simple goiter to be 93 in girls and 7 in boys. The basal metabolic rate was normal (between 10 plus

and 10 minus) in 74%. The majority of the cases tended to a low normal and down to minus 18%, showing that simple goiter nearly always is associated with some degree of hypothyroidism. Symptoms of thyroid hyperactivity were noted in 16 with a basal metabolic rate above 10 consisting of nervousness, tremor, tachycardia and enlargement of the thyroid. All of these symptoms pass when puberty is established. An erroneous diagnosis of exophthalmic goiter is sometimes made and strenuous treatment instituted. The condition in New York City is not due to a lack of iodine in the food or water supply but rather to exhaustion of the normal amount of thyroxin due to sustained metabolic stress.—M. B. G.

XXXII. Function of the normal thyroid at different ages and changes from the normal under pathological conditions (Ueber die Abhaengigkeit der Funktion der Schilddruese vom Lebensalter und von Krankhaften Zustaenden). Vogeler, K., Arch. f. klin. Chir. **157**: 704. 1929.

Vogeler used the tadpole method to test the potency of normal and pathological thyroids. Studying the latter only Wegelin and Abelin, deQuervain and others had observed that the various types did not exert the same degree of influence on tadpoles. Exophthalmic glands showed the greatest potency, normal glands were next in potency, parenchymatous struma and fetal hyperplasia were less, while cretinoid glands were hardly potent. Vogeler used a more exact quantitative method of observation. He fed powdered gland plus lactose and determined the minimum effective dose of each gland. The animals were subjected to the thyroid influence only once over 2 days, and then observed for 2 weeks. Every hyperplasia shows its specific minimum effect, i.e., glands exhibiting the same histological picture and of similar clinical symptomatology differ in potency. In general, the potency seems to increase with age. Vogeler, therefore, found it advisable to correlate age with potency and made some observations on normal human glands, ranging from the 6th fetal month up to 79 years. A very low degree of potency is noticeable during the 6th fetal month; potency increases towards birth. After birth, a stationary condition exists for over one month (which seems to indicate previous material supply). There is a decrease up to the 5th month, then, increase to birth level at the end of the 1st year; very slight increase up to the 10th year and considerable increase up to 15th. This high level which is surpassed only by pathological glands is maintained into the 5th decade, when there is a drop, especially in the female. There is a further gradual increase continuing into old age. From birth on the female potency curve differs from the male, except in old age. It shows far greater periodic fluctuations and, in general, higher values, but is considerably lower during the climacterium. Thus, there is in both sexes a high peak at birth, a much higher during puberty and a still higher, but constant level, during old age. In the female, there is a sharp rise after the previous fall of the climacterium. It is well known that obesity and slight myxedema are often remedied after the menopause. Two goiter forms are most pronounced, pubertal and climacteric. By this method, Vogeler found that both fall below the normal potency levels of those periods. This explains the hypertrophy as an attempt at physiological compensation.

—F. Gudernatsch.

Hepatic lesions associated with exophthalmic goiter. Weller, C. V., Tr. A. Am. Physicians, **45**: 71. 1930.

A well-marked chronic parenchymatous hepatitis was found at autopsy in 22 of 44 selected cases of Graves' disease while but one example was found in a control series of the same number of autopsies. In the Graves' disease group, only 6 showed no hepatitis, while of the control series 30 out of the total of 44 showed no hepatitis. The coincidence of hepatitis with exophthalmic goiter is therefore significant and is in accord with clinical observations of the occurrence of jaundice in occasional cases of Graves' disease.—I. B.

A biological reaction for hyperthyroidism. Willis, D. A. and J. M. Mora, Proc. Soc. Exper. Biol. & Med. **28**: 562. 1931.

A modification is proposed for the Dresel reaction test for hyperthyroidism. Mice are injected with serum from the patient or animal to be tested, fed carbohydrate and water for 30 hours, starved for 16 hours, then injected with 1.5 cc. of 10% glucose solution and killed 3 hours later. The liver is quickly removed, and by a simple technic is tested for the presence of glycogen. Serum

from toxic goiter patients generally renders the liver of the mouse glycogen poor, while serum from normal individuals leaves the liver rich in glycogen. The authors believe that this offers possibilities as a delicate biological test and means of study in borderline cases of hyperthyroidism, and an aid in controlling experimental hyperthyroidism.—M. O. L.

Changes in the skin in thyrotoxicosis. With a brief study of the absorption time of intradermally injected salt solution in patients with thyrotoxicosis. Youmans, J. B., Am. J. M. Sc. **181**: 681. 1931.

The author believes that the smooth, thin and moist skin seen in thyrotoxicosis is due to improved metabolism caused by increased blood flow. This also accounts for the good general condition of the skin and subcutaneous tissue. Usually there is an increase in pigmentation of the skin but not of the mucous membrane. There is no increase in pigmentation about such areas as the nipples, axillae and genitals. No reason is given for the decrease in amount of hair. The increase in temperature of skin, and increase of moisture on the skin is proportional to the increase in metabolic rate. In the small series examined, the absorption time for the intradermally injected salt solution was longer in the Negro than in white persons.—E. L.

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Your doctor is not a superman or a magician. He is a human being, with human sympathy and understanding, working within the limits of scientific knowledge. But he achieves victories today which, only a few generations ago, would have been called miraculous.

With the help of modern scientific equipment, with a fund of co-ordinated medical and surgical knowledge undreamed of even by our grandfathers, *your* doctor can *prevent* diseases that were once supposed to be the natural heritage of mankind. He can *cure* diseases which were once unqualifiedly labeled "fatal".

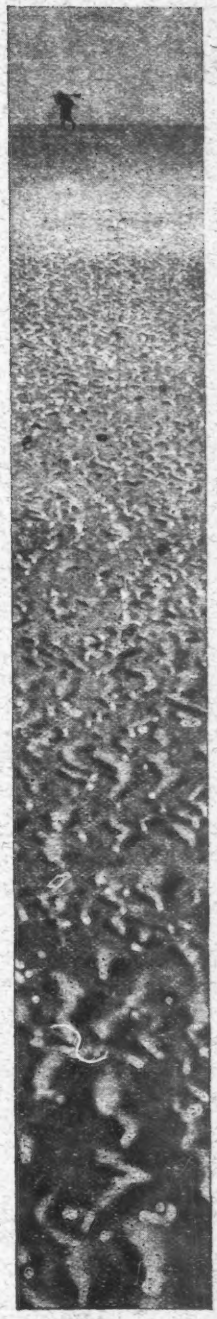
But he can do these things only with your co-operation. To *get* his help, you must *seek* it.

The better he knows you, the more he can do for you. That is why it is short-sighted and wasteful to wait until an emergency *compels* you to see him. Regular health examinations are not costly—they are economical. They reveal—to the one man who can help you—the weak spots in your health-armor which need strengthening.

See your doctor before he has to see you.

PARKE, DAVIS & COMPANY
DETROIT, MICHIGAN

The World's Largest Makers of Pharmaceutical and Biological Products



MAXIMUM AND UNVARYING POTENCY

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ARMOUR'S Thyroid finds its principal source in the thyroid glands of domestic food animals. A prodigious number of these and other food animals are slaughtered daily in the Armour Packing Plant. From this vast amount of raw material, the Armour Laboratories are enabled to make a fastidious selection of glands.

These glands are processed as they come fresh from the killing floor, with the animal heat still present. The active principles are thus preserved without injury. You can be sure at all times of maximum and unvarying potency in Armour's Thyroid, as well as in all organotherapeutic preparations bearing the Armour name and label. In more than a third of a century of extensive service, not one product of the Armour Laboratories has been found wanting in potency.

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Thyroid therapy is indicated in simple goiter, cretinism and myxedema. Medication for the two latter conditions must be continued throughout life. In small thyroid insufficiency the results obtained by thyroid medication usually are lasting. Armour's Thyroid: powder, 2, 1, 1/2, 1/4, and 1/10 grain tablets.

Among other Armour organotherapeutic products are Armour's Pituitary preparations, Suprarenalin Solution, Concentrated Liver Extract. Assure yourself of Armour dependability by specifying the Armour name for your organotherapeutic preparations.

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"Headquarters for medical supplies of animal origin"